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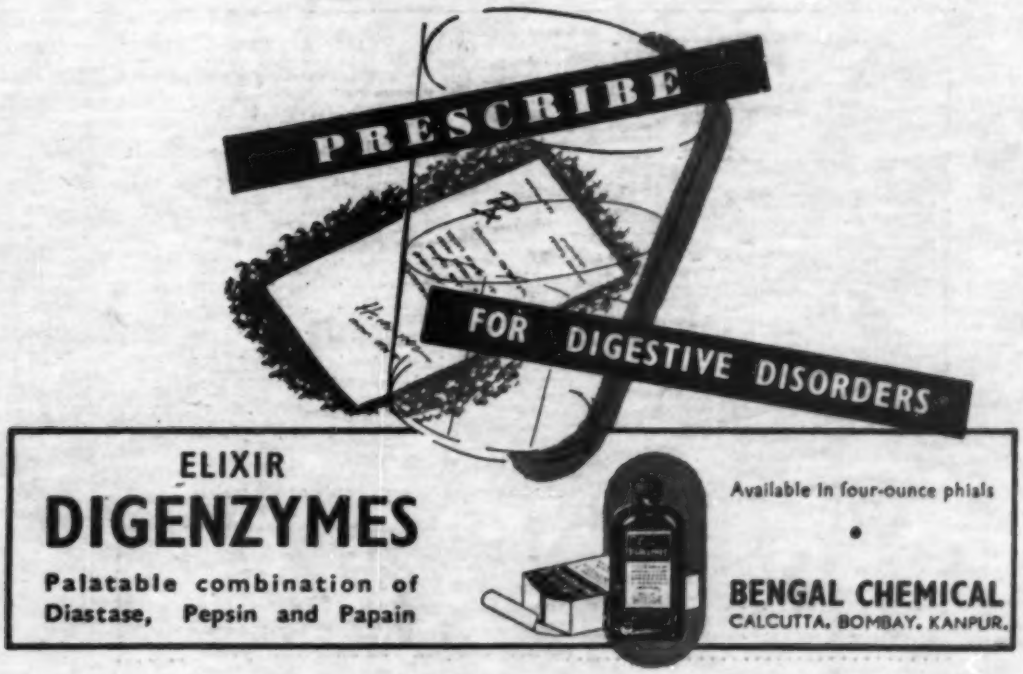

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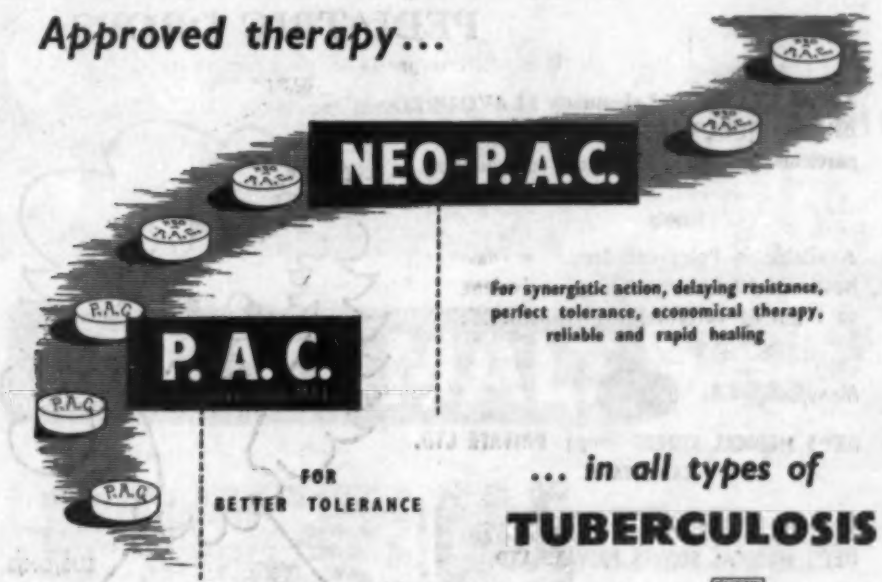

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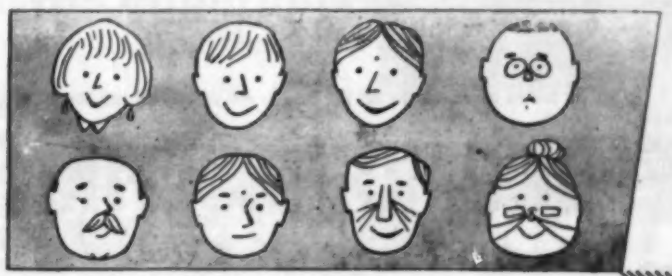

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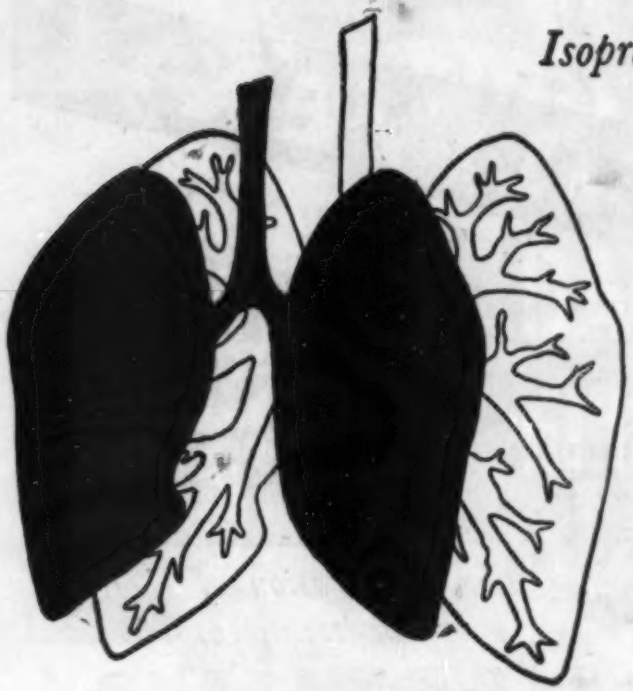

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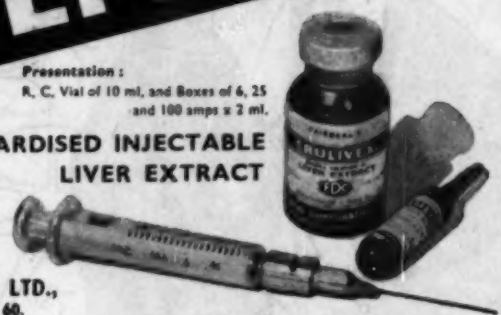

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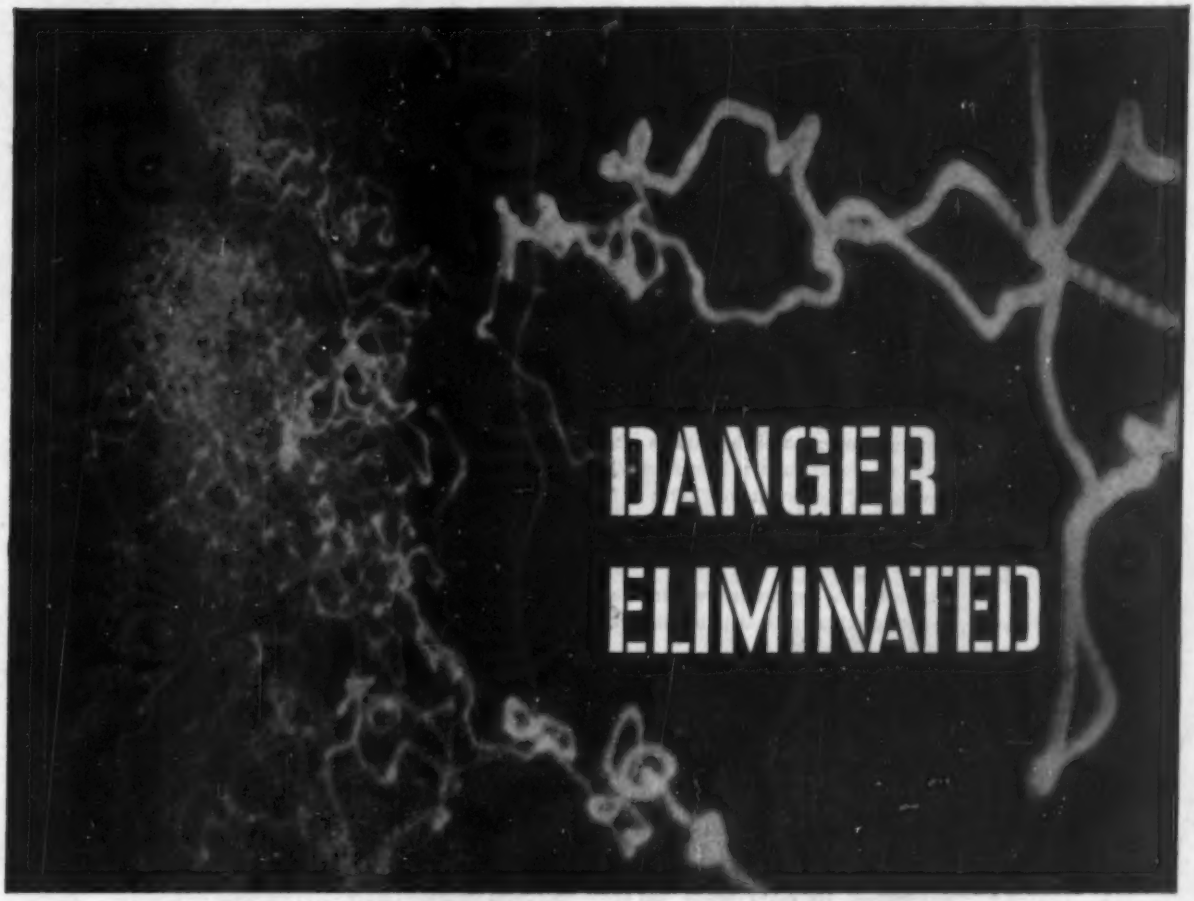

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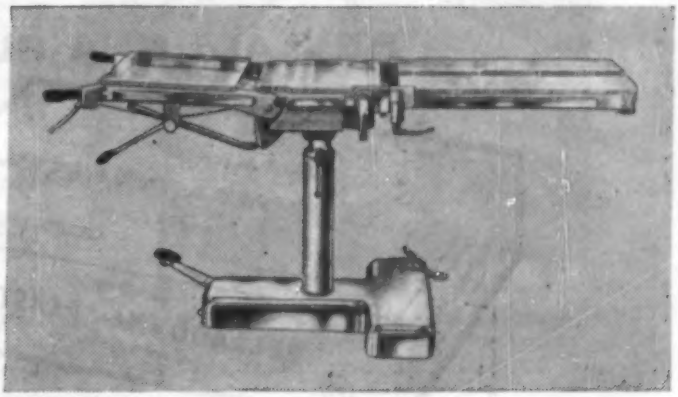

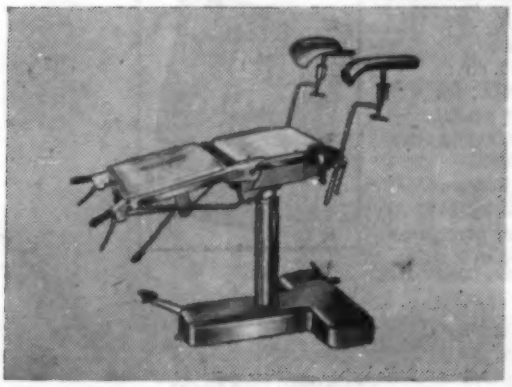

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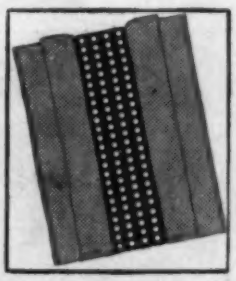

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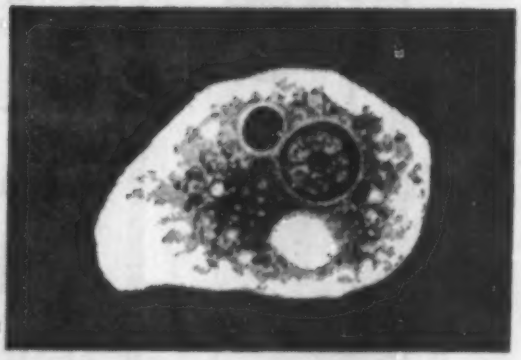

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ORIGINAL ARTICLES

ANAEMIA IN CIRRHOSIS OF THE LIVER—A CLINICAL STUDY

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Since the first report by Hayem in 1889, the association of anaemia with cirrhosis of the liver has been established by both clinical and experimental studies by many investigators. There is no unanimity in their observations on the extent and nature of anaemia, and the pathogenesis still remains unexplained.

Hypervolaemia (Bateman *et al*, 1949), hypersplenism (Hyman and Southworth, 1951 ; Jones *et al*, 1955), excessive haemolysis (Jandl, 1955 ; Sen Gupta and Aikat, 1959), defective storage of antianaemic principle (Wintrobe and Shumacker, 1933) and its defective elaboration (Davidson and Fullerton 1938), defective blood generation from the marrow (Minot, 1936), and malnutrition (Sen Gupta and Aikat, 1959) have all been advanced as the possible factors in its causation.

We have reported on our observations on the experimentally induced cirrhosis of the liver in albino mice (Mathur *et al*, 1960). This work has now been extended to the clinical study of anaemia in cirrhosis of the liver.

This paper deals with our observations on the incidence, morphology and severity of anaemia in patients suffering from cirrhosis of the liver. A reassessment has been made of some of the factors involved in its pathogenesis.

MATERIAL AND METHODS

Fifty cases of cirrhosis of the liver admitted to the Sarojini Naidu Hospital, Agra were investigated. These included 33 males and 17 females ; the youngest in the group was 10 years of age and the oldest 60 years, with an average of 34·9 years. The clinical diagnosis was confirmed by liver biopsy in twenty cases and at autopsy in two of them. All cases with a history of bleeding and associated with other diseases likely to cause anaemia have been excluded from the present study.

Peripheral blood examinations, including erythrocyte count, haemoglobin value, packed cell volume, mean corpuscular values, colour index, reticulocyte count and fragility test, were carried out in all the patients.

The cytology of bone marrow obtained by sternal aspiration was studied in forty-eight cases.

Liver biopsy material was obtained in twenty cases using Vim Silverman needle by the intercostal route. The assessment of the degree of cirrhosis was based chiefly on the degree of fibrosis and atrophy of liver cells according to the following schedule :

Grade I cirrhosis, traces of fibrosis.
Grade II cirrhosis, definite fibrosis plus atrophy of hepatic cells.

Grade III cirrhosis, fibrous tissue equals hepatic parenchyma.

Grade IV cirrhosis, fibrous tissue exceeds hepatic parenchyma.

Fractional test meal was done in thirty-six cases using 7 per cent of alcohol as test meal. Plasma volume was determinated by Evans blue (T-1824) dye dilution method of Gregerson (1944) in five out of eight cases of normocytic normochromic anaemia. Urine urobilinogen was estimated in all cases.

All studies were made shortly after hospitalisation of the patients, before institution of specific therapy.

Observations

Incidence of anaemia—Of the fifty cases studied, 7 had haemoglobin within normal limits (12-14·5 g. per cent), while the remaining 43 had haemoglobin below 12 g. per cent, giving an incidence of anaemia as 86 per cent.

Severity of anaemia—Of the forty-three anaemic patients, 17 (34 per cent) were mildly anaemic (haemoglobin 9-12 g. per cent), 21 (42 per cent) were moderately anaemic (haemoglobin 6-9 g. per cent) and 5 (10 per cent) were severely anaemic (haemoglobin below 6 g. per cent). Most of the cases (76 per cent) showed mild to moderate degree of anaemia. The erythrocyte count ranged from 0·96 to 4 mill./c.mm.

Severity of anaemia and extent of liver damage—The degree of anaemia and extent of liver damage as judged from histological examination of the biopsy specimen in twenty cases were found to have no correlation (Table 1).

Table 1—Showing Degree of Anaemia in Various Grades of Cirrhosis of the Liver

Grades of cirrhosis	No. of cases	Average Hb. (g.%)	Average M.C.H.C. (%)
I	4	8·0	26·68
II	4	11·7	30·1
III	5	9·5	30·74
IV	7	7·8	28·7

Morphology of anaemia—Morphologically two different forms of anaemia, viz., macrocytic (cases having M.C.V. above 94 $c\mu$, the highest normal limit) and normocytic were observed. Microcytic anaemia was not encountered in any case of the present series. The macrocytic anaemia was observed in 54 per cent (27 cases) and normocytic in 32 per cent (16 cases) while the remaining 14 per cent were not anaemic. The average haematological values are given in Table 2.

Table 2—Showing Average Haematological Values in Various Types of Anaemia

Morphology of anaemia	No. of cases	Average Hb. (g. %)	Average R.B.C. (m/c. mm.)	Average P.C.V. (%)	Average M.C.V. (c.μ)	Average M.C.H. ($\mu\mu$g.)	Average M.C.H.C. (g.%)
Macrocytic :							
Orthochromic	14	8·4	2·46	27	110	35	32
Hypochromic	13	7·88	2·89	31	109	27	28
Normocytic :							
Orthochromic	8	8·2	2·82	25	90	29	33
Hypochromic	8	8·1	3·48	30	86	23	27

Reticulocyte count—The reticulocyte count, done in 13 cases only, was within normal range of 0·5 to 1·5 per cent. Out of these 13 cases, only 2 had macrocytosis peripherally.

Blood volume and plasma volume—The estimations of blood volume and plasma volume were done in 5 out of 8 cases of normocytic normochromic anaemia (Table 3).

Table 3—Showing Plasma Volume, Blood Volume and R.B.C. Volume in Cases of Normocytic Normochromic Anaemia

Name of patient	Blood volume (% body weight)	Plasma volume (% body weight)	R.B.C. (volume)	P.C.V. (%)	Hb. (g. %)
N. ...	10·25	7·72	2·53	26	9·0
K.S. ...	6·0	3·76	2·24	17	5·5
M.L. ...	7·34	6·59	1·75	20	6·5
K.D. ...	11·55	8·59	2·96	23	8·5
V.P. ...	12·89	9·14	3·75	31	10·0

The plasma volume was not consistently increased in all cases. Only 3 cases showed a definite increase. Though the red cell mass was within normal range in these cases, it was found to increase with the rise in the plasma volume.

Fractional test meal—This was studied in 36 out of 50 cases. Achlorhydria was observed in 12 cases ; nine of them showed macrocytic anaemia, while 3 showed normocytic anaemia. Nine cases had hyperchlorhydria ; out of which 5 were of macrocytic anaemia and 4 of normocytic anaemia. The remaining 15 had acid content within normal range.

Fragility of R.B.C.—The fragility of R.B.C. was within the normal range in all the 50 cases.

Urine urobilinogen—Urine urobilinogen of 45 cases was within the normal range.

Bone marrow cytology—The bone marrow cytology was studied in 48 cases and results were analysed as regards the differential count and morphological abnormalities of various groups of cells.

MYELOID : ERYTHROID RATIO—The M : E ratio was below the lowest normal limit of 2 : 1 in 23 cases. In 2 of them the M : E ratio was reversed (0·1 : 1 and 0·8 : 1). 18 cases had M : E ratio between 2 : 1 and 3 : 1, 4 between 3 : 1 and 4 : 1 ; and 3 above 4 : 1.

DISTRIBUTION OF ERYTHROID SERIES OF CELLS—All cases except 5 showed moderate or marked erythroblastic hyperplasia. Twenty-five cases had marked erythroblastic hyperplasia, the nucleated cells exceeding 30 per cent of the total cells counted. The rest of the cases which showed moderate hyperplasia had nucleated erythroid cell count between 20 and 30 per cent. All cases except 8, who showed marked erythroblastic hyperplasia, showed maturation arrest at the early normoblast (basophilic normoblast) stage.

QUALITATIVE CHANGES IN ERYTHROBLASTS—Qualitative changes in the erythroblasts were found in 7 cases. The changes included increase of the size of the normoblasts in all developmental stages, increase of nuclear size and a disturbance of nuclear cytoplasmic ratio. The normoblasts were large in size, but the nuclear pattern was essentially that of normoblasts. The nuclear cytoplasmic ratio was altered in favour of relative increase of cytoplasm. The increase in cytoplasm was not as marked as seen in megaloblasts and the large cells were of the type designated macronormoblasts by Jones (1943). These 7 cases showed macrocytosis peripherally. In the rest of the 17 cases which showed macrocytosis peripherally macronormoblastosis or megaloblastosis was not observed in the bone marrow.

GRANULOCYTES AND MONOCYTES—The differential distribution of cells of granulopoietic and monocytic series was within normal range except in 4 patients who showed marked increase in the neutrophilic myelocytes. No qualitative change was detected in the granulocytes and monocytes.

EOSINOPHILS—The differential distribution of eosinophils had no significant deviation from the normal except in 2 cases who showed an increase to 5 and 7 per cent respectively.

LYMPHOCYTES—The marrow contained the normal incidence of lymphocytes except in one patient who showed lymphopenia of 2 per cent and 4 cases who showed lymphocytosis of 18, 16, 16 and 18 per cent.

PLASMA CELLS—The frequency of plasma cells was found to be below 2 per cent in all cases except in 7 who showed increase of plasma cells from 4 to 6 per cent.

RELATION BETWEEN M : E RATIO AND SEVERITY OF ANAEMIA—The M : E ratio on an average was found to decrease as the severity of anaemia increased (Table 4).

TABLE 4—SHOWING RELATION BETWEEN M : E RATIO AND SEVERITY OF ANAEMIA

Severity of anaemia	No. of cases	Average M : E ratio
No anaemia (Hb. above 12 g. %)	7	3·5 :1
Mild anaemia (Hb. between 9-12 g. %)	17	2·74 :1
Moderate anaemia (Hb. between 6-9 g. %)	21	1·64 :1
Severe anaemia (Hb. below 6 g. %)	5	1·6 :1

DISCUSSION

Though anaemia has been a common finding in cirrhosis of the liver, wide variations in its incidence have been observed by different workers ranging from 43 per cent reported by Rosenberg and Walters (1936) to 100 per cent reported by Huang and Wang (1949). The incidence of 86 per cent in the present series is in agreement with Wintrobe (1936) and Berman *et al* (1949) and corresponds closely to Jarrold and Vilter (1949). The incidence of anaemia reported by various authors is given in Table 5.

TABLE 5—SHOWING INCIDENCE OF ANAEMIA IN CIRRHOSIS OF THE LIVER AS REPORTED BY VARIOUS AUTHORS

Authors	No. of cases studied	No. of cases showing anaemia	Incidence of anaemia (percentage)
Rao (1933)	64	43	66·6
Wintrobe (1936) ...	44	37	84
Rosenberg (1936) ...	—	—	42
Jarrold & Vilter (1949) ...	30	24	80
Huang & Wang (1949) ...	32	32	100
Berman *et al* (1949) ...	25	21	84
Mehrotra (1957) ...	32	29	90·6
Wilhelm *et al* (1958) ...	73	44	60
Sen Gupta & Aikat (1959)	53	53	100
Present Authors (1960) ...	50	43	86

Our observations regarding the severity of anaemia are in conformity with the findings of Cheney (1933), Wintrobe and Shumacker (1933), Bloomfield (1938), Fernando *et al* (1948) and Mario (1951) who reported moderate degree

of anaemia in the majority of their patients and severe degree of anaemia in only a small proportion of cases.

The degree of anaemia could not be correlated with the extent of liver damage (Table 1). Observations similar to ours have been reported by Berman *et al* (1949) and Whilhelm *et al* (1958). Dietetic imbalance which is a common accompaniment of cirrhotics may probably add to the severity of anaemia, leading to this disparity between the degree of anaemia and the amount of liver damage.

Morphologically macrocytic and normocytic anaemia were observed in 54 and 32 per cent of the cases respectively in the present series. Though wide variations in the percentage distribution of the various types of anaemia have been reported, the macrocytic and normocytic anaemias have been reported to be commoner than the microcytic variety (Berman *et al*, 1949 ; Huang and Wang, 1949 ; Sen Gupta and Aikat, 1959). Microcytic anaemia has been reported only in cases with chronic haemorrhage of long duration (Bianco and Joliffe, 1938).

Bone marrow changes, in the form of increased erythropoietic response and hence diminution in the M : E ratio, as observed in the present series have been reported by most of the workers (Berman *et al*, 1949, Leitner *et al*, 1949, Jones *et al*, 1955 and Sen Gupta and Aikat, 1959). This preponderance of erythropoietic elements in the bone marrow can be explained on the basis of compensatory hypertrophy as a result of increased demand on haemopoietic tissue consequent on anaemia resulting from liver dysfunction.

The increased plasma cells in the bone marrow of 7 cases is in conformity with the observations of Limarzi *et al* (1943) and Jarrold and Vilter (1949). The significance of the increase of plasma cells is not clear but as plasma cells are responsible for synthesis of globulins and since cirrhosis of the liver is characterised by hyperglobulinaemia, it is reasonable to expect a rise in these cells in this condition. Sen Gupta and Aikat (1959) observed a correlation between increased plasma cells and hyperglobulinaemia in a fair number of their cases. The nature of the stimulation for its occurrence, however, awaits further study.

Pathogenesis of anaemia—The pathogenesis of anaemia in cirrhosis of the liver has not been clearly defined. There are multiple factors responsible for the mechanism of its production as no single morphological form of anaemia has been noted in cirrhosis. Moreover, a significant number of patients does not have appreciable anaemia.

Many a time anaemia in cirrhosis of the liver has been demonstrated to be apparent due to hypervolaemia (Bateman *et al*, 1949 ; Mehrotra, 1957). Our observations, however, do not explain hypervolaemia as the cause in the genesis of anaemia because plasma volume was not consistently increased in all cases (Table 3) and red cell mass, though found within normal limits, was also raised as the plasma volume increased. These observations are in full agreement with those of Hyde (1952) and Berlin *et al* (1952). Sen Gupta and Aikat (1959) are, however, of the opinion that hypervolaemia may be a contributory factor in enhancing the degree of anaemia in some cases of cirrhosis of the liver.

Increased attention has been paid to the haemolytic character of anaemia in cirrhosis of the liver. This belief is based on the observations of increased reticulocytosis (Rosenberg and Walters, 1936), increased concentration of red cell precursors in the marrow (Jandl, 1955), extension of bone marrow organ (Eppinger, 1920 ; Berman *et al*, 1949), increased rates of urobilinogen excretion (Watson, 1937 and 1939 ; Sen Gupta and Aikat, 1959), increased rate of destruction of red cell (Chaplin and Mollison, 1953 ; Jones *et al*, 1955) and increased fragility of red cells (Shen *et al*, 1944). We were, however, not able to find reticulocytosis in any of the 13 cases examined. The urobilinogen excretion and fragility of red blood corpuscles were also within normal range in all the cases studied. Yet, increased haemolysis as the cause of anemia cannot be ruled out on the basis of these observations alone, because definite and marked increase in the concentration of red cell precursors was observed in 25 cases, so much so that M : E ratio was reversed in 2 cases. This diversity of observations in the present series can be explained on the suggestion of Hyman and Southworth (1951), that low grade haemolysis may occur regularly in cases of cirrhosis which may not be detected by routine biochemical investigations. The exact mechanism involved in the process of haemolysis is not well understood. A number of postulates put forward to explain it is beyond the scope of this paper to discuss.

In view of our observation of increased erythropoietic response of the bone marrow and a definite relation between the M : E ratio and degree of anaemia (Table 4), the explanation of failure of bone marrow due to accumulation of toxic products as a result of liver dysfunction (Minot, 1936) does not appear to be cogent. Davidson and Fullerton (1938) and Berman *et al* (1949) have also denied this concept of anaemia in cirrhosis of the liver.

In 1933 Wintrobe and Shumacker suggested that the anaemia may be due to the inability of a chronically and extensively diseased liver to store the anti-anaemic principle. This view was later sup-

ported by Goldhammer *et al* (1934), Wilkinson and Klein (1934) and Movitt (1950). Later Jarrold and Vilter (1949), Hall (1956) and Krasnow *et al* (1957) suggested deficiency of the extrinsic factor. The possibility of these defects does not exist in the present series, as the bone marrow did not show megaloblastic response and changes in myelocytic series of cells (typical of pernicious anaemia) in any of our cases. The achlorhydria observed in 9 cases of macrocytic anaemia is of little significance as it was observed in 3 cases of normocytic anaemia as well. It may be due to chronic portal congestion as suggested by Davidson and Fullerton (1938).

Macronormoblastosis in sternal marrow smear examination can explain peripheral macrocytosis in 7 of the cases of macrocytic anaemia. Macronormoblastosis has also been reported by Huang and Wang (1949) and Berman *et al* (1949). What factors play a part in its causation, however, needs further study. The absence of any dysplasia in the bone marrow in the remaining 36 macrocytic individuals support the view that macrocytosis is peripheral rather than central. Rosenberg and Walters (1936) suggested that reticulocytes in large number might be responsible for macrocytosis. None of the 13 cases studied in the present series had increased reticulocyte count, though 2 cases had peripheral macrocytosis. Sen Gupta and Aikat (1959) had also observed normal reticulocyte count in their series except in one case.

Osmotic pressure disturbances in the plasma due to disturbances in plasma proteins or retention of salts of bile acid as suggested by Meulengracht and Gormsen (1948) does not seem tenable because we observed elevated colour index and M.C.H.C. which would not have been the case, had the plasma factor caused simple swelling of erythrocytes.

The cause of the anaemia and macrocytosis remains obscure, but we agree with the suggestion of Hall (1956) that the cause of macrocytosis is definitely the liver damage (Mathur *et al*, 1960) and it is not due solely to increased number of reticulocytes, swelling of erythrocytes, or dietary deficiencies, although these may be contributory factors.

Summary

Anaemia has been studied in fifty clinically diagnosed cases of cirrhosis of the liver. The diagnosis was confirmed after biopsy in twenty cases and after autopsy in two of them.

The incidence of anaemia was 86 per cent—54 per cent being macrocytic and 32 per cent normocytic. Most of the patients had mild or moderate anaemia. No relation between the severity of anaemia and the extent of liver damage was observed.

Bone marrow changes have been in the form of marked or moderate degree of normoblastic response. Seven cases had macronormoblastosis.

The pathogenesis of anaemia has been discussed. The role of hypervolaemia, excessive haemolysis, deficiency of antianaemic principle, increased incidence of reticulocytes, and swelling of erythrocytes have all been considered, but no definite conclusion could be drawn. It has been suggested that anaemia is secondary to liver dysfunction.

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FURTHER CLINICAL EXPERIENCE WITH ORAL HYPOGLYCAEMIC AGENTS
(Observations on the Results)

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Tolbutamide (D-860, Rastinon, Artosin), the oral hypoglycaemic agent, is being widely used in the treatment of maturity onset type of diabetes mellitus. Work has been done in this laboratory to determine the mechanism of action of carbutamide (BZ-55), and tolbutamide (Aiman and Kulkarni, 1957 ; Aiman and Chaudhary, 1959), and to carry out a controlled study of their effects in suitable clinical cases. Short-term clinical studies with carbutamide have been previously reported (Kulkarni and Aiman, 1958). Therapy was continued in some of these patients, and since tolbutamide is much less toxic than carbutamide, these patients were switched over to tolbutamide. Patients subsequently admitted were treated with tolbutamide only. A six months' follow-up of three cases with carbutamide and five cases with tolbutamide are reported. In addition, other patients were treated with tolbutamide but they failed to respond to the drug. The latter are included in the discussion so far as they bring out particular features of treatment with these hypoglycaemic agents.

* Undertook part of this work during the tenure of a Government of Bombay Research Grant.

MATERIAL AND METHOD

The patients were under observation in the Sassoon Hospitals, Poona. The initial stabilisation and the various biochemical tests including the glucose tolerance test were carried out as reported earlier (Kulkarni and Aiman, 1958). The initial dosage also was similar to that employed previously with BZ-55. Treatment with tolbutamide was checked by fasting blood sugar (F.B.S.) estimations every 3 to 4 days until a satisfactory response was obtained or no response was obtained within a reasonable period of time. In the former case the dosage of the drug was adjusted so that the F.P.S. remained between 100 and 120 mg. per cent and on stabilisation at this level the patients were discharged from the hospital and the undermentioned follow-up was done: An overnight admission once every month for a F.B.S. estimation and urine examination next morning and a general check-up (weight etc.), the findings being recorded. At the end of six months of therapy a repeat biochemical examination and glucose tolerance test were carried out. All the long-term cases have been under treatment for at least six months, the longest period of study was thirty-four months.

The usual dosage schedule for the drug was the same as previously reported (Kulkarni and Aiman, 1958) except in two cases as noted below.

RESULTS

Out of the twenty-seven cases admitted only 16 were selected for treatment with these oral hypoglycaemic agents, as the rest of the patients were juvenile diabetics aged between 15 and 25 years. The majority of selected cases were 40 years or above. Only one patient gave the family history of diabetes mellitus.

We obtained similar results (Table 1) as reported by previous workers, but certain interesting points emerged from this study. Our results were similar in the sense that favourable response was met with in elderly obese patients (12 out of the 16 cases were 40 years or above, the others were between 37 and 38 years of age) with low insulin requirements and that the drug was ineffective in juvenile diabetics. The drug on the whole was well tolerated by the majority of patients. The interesting features peculiar to our study were in relation to the stress of systemic infection, comparative efficacy of carbutamide and tolbutamide, variability of the maintenance dose of tolbutamide, and the usefulness of tolbutamide in diabetes complicated with hypertension. Case 4 (Table 1) had been suffering from hypertension for the last 6 years, his blood pressure on admission was 162/100

TABLE 1—SHOWING SALIENT FEATURES OF THE CASES STUDIED

Case No.	Sex	Age (years)	Duration of diabetes	Height (inches)	Weight (lb.)	Previous insulin requirement	Response to treatment		F. B. S. (mg. per cent)		Dose of stabilisation	
							D-860	BZ-55	Initial	After stabilisation	D-860	BZ-55
1.	M	40	2 years	65	90	Nil	Good	Good	200	106	0·5	0·25
2.	M	38	20 days	61	108	Nil	Nil	Good	126	113	—	0·5
3.	M	39	6 months	61	103	10 units plain, B.D.	Good	N.T.	140	99	0·5	N.T.
4.	M	54	3 weeks	71	174	5 units plain+zinc protamine 3 units O.D.	Good	N.T.	340	100	0·3 alternate day	N.T.
5.	M	39	6 months	66	119	Nil	Good	Good	145	114	0·5	N.M.
6.	F	45	2 months	57	116	Nil	Good	Good	185	106	0·5	0·5 alternate day
*7.	F	55	6 months	63	108	Nil	Good	N.T.	172	100	0·5	N.T.
8.	M	48	3 years	64	96	10 units plain, B.D.	Nil	Nil	278	—	—	—
*9.	F	67	4 years	65	130	10 units plain, B.D.	Good	N.T.	200	120	0·5	—
*10.	M	43	2 months	56	115	Nil	Good	N.T.	132	111·5	0·5	—
*11.	F	50	2 years	58	126	Nil	N.T.	Good	207	102	N.T.	0·5
12.	F	40	?	60	117	Nil	N.T.	Good	135	108	N.T.	0·5
13.	M	37	?	65	81	Nil	N.T.	Nil	270	—	—	—
14.	M	43	8 days	65	130	Nil	N.T.	Good	125	102	N.T.	0·5
15.	M	40	2 years	68	120	Nil	N.T.	Nil	280	—	N.T.	—
16.	M	48	8 years	66	125	20 units plain, B.D.	N.T.	Nil	288	—	N.T.	—

Note—Cases marked with asterisk could not be followed up for 6 months;
Case 1 developed pneumonitis while Cases 2 and 6 developed granulocytopenia during treatment.
N.T. = Not tried; N.M. = Not maintained.
Amounts of D-860 and BZ-55 indicate daily dose unless otherwise mentioned.

mm. Hg. For this complication we treated him with raudixin, 50 mg. daily.

Systemic infection during therapy—In the case of a patient who was on carbutamide therapy and responded remarkably well to it, while he was successfully controlled had two attacks of pneumonitis at an interval of 8 weeks. On both occasions prior to the attacks the patient was well stabilised, but with each attack his F.B.S. rose and remained high for about two weeks. During the attack the patient was treated wih antibiotics, and the carbutamide dosage was raised. He recovered from the acute illness in a few days, but the blood sugar level remained high for about two weeks inspite of the raised dosage of carbutamide. No insulin was given and complete control was finally re-established on the initial maintenance dose.

Comparative efficacy of carbutamide and tolbutamide—The half life of tolbutamide being much shorter than that of carbutamide the maintenance dose of the former is usually higher than that of the latter. We noted the same thing. We also observed that when a switch over was made from carbutamide (maintenance dose 0·5 g, once daily) to tolbutamide a larger maintenance dose (1·5 g.) was required, in fact in Case 2 (Table 1) we failed, even with a higher dosage schedule, to produce a satisfactory control of hyperglycaemia and were forced to revert to carbutamide. Unfortunately facilities for estimation of the blood level of tolbutamide were not available in this hospital.

Maintenance dose—We found that the dose required to maintain the diabetics in a stable condition had no relation to the severity of the disease as judged by the initial F.B.S., glucose tolerance test and the insulin requirement of the patient.

In two cases we found a high initial blood sugar (F.B.S. above 300 mg. per cent) and even ketosis; in one (Case 4) when the patient was stabilised on a diabetic diet and insulin (Table 1), the ketosis diminished and the patient responded remarkably

well to therapy with tolbutamide. He had been maintained satisfactorily on 0·3 g. every alternate day—a remarkably small dose for tolbutamide. The second case, as reported previously (Kulkarni and Aiman, 1958), was satisfactorily maintained on 0·25 g. carbutamide daily. Hence ketosis as a transitory acute episode due to complete lack of control or recognition of the diabetic status, as in both these cases, is not necessarily a contraindication to sulphonylurea therapy.

Case 2 (Table 1) whose disease was only recently detected and which appeared to be mild as judged by his F.B.S. (126 mg. per cent) and the absence of ketosis, required an astonishingly high dose (1·5 g. carbutamide for 10 days after routine initial dose) to bring him under control.

Development of granulocytopenia with carbutamide—Two of our patients developed mild granulocytopenia with carbutamide after 8 to 9 months. Counts in Case 2 (Table 1) are: Total W.B.C. 5400/c.mm. and polymorphs 36 per cent, lymphocytes 54 per cent, eosinophils 6 per cent, monocytes 3 per cent, basophils 1 per cent and in Case 6 (Table 1) total W.B.C. 4100/c.mm., polymorphs 45 per cent, lymphocytes 50 per cent, eosinophils 3 per cent, monocytes 0 per cent, basophils 2 per cent, but the patients recovered on discontinuing the drug and on receiving folic acid and vitamin B_{12}.

Glucose tolerance test—The pattern of the glucose tolerance curve did not change considerably, after long-term therapy with carbutamide or tolbutamide, though it ran at a lower level as reported previously (Kulkarni and Aiman, 1958).

Discussion

During the last five years the hypoglycaemic sulphonylureas have been used extensively all over the world. Tolbutamide which is comparatively much less toxic seems to have replaced carbutamide. It is our experience that the type of severe agranulocytosis which is not uncommon according to foreign reports (Jackson and Herman, 1956 ; Kirtly, 1957) is not seen here so frequently with carbutamide. There are only a few comparative studies with these drugs in India, but from our results it is apparent, that the maintenance dose of carbutamide (0·25 to 0·5 g.) is approximately half that of tolbutamide (0·5 to 1 g.) for an average patient. The cost of the two drugs being the same it makes a material difference to a particular patient which drug is used. Carbutamide is a toxic drug, and where the cost of treatment is immaterial tolbutamide should be preferred, but for a poor patient carbutamide may prove more practicable. Moreover, in two patients carbutamide (0·5 g.) succeeded in controlling diabetes resistant to high dosage (1·5 g. for 8 days after the initial dosage) of tolbutamide. Therefore, we consider it advisable to try carbutamide in cases suitable for oral therapy, but which do not respond to tolbutamide, and thus perhaps avoid the trouble of insulin therapy. It is our impression that carbutamide still retains a limited place for cautious use in the treatment of diabetes mellitus.

As a large number of long-term trials are being reported, cases of delayed failure are being noticed (Mehnert *et al*, 1958). Diabetes is a progressive condition and it is a common experience that with the passage of time insulin dosage has to be increased due to progressive diminution of endogenous insulin. Since endogenous insulin is necessary for the action of sulphonylureas, this natural progress of disease may progressively diminish the responsiveness to these drug. Cases have been reported where resistance developed in a space of a few months (Duncan, 1958 ; Dolger, 1958). Here the above explanation is unlikely. It is increasingly being believed that the sulphonylureas act by stimulating the *beta* cells. It is possible that this initial stimulation leads to exhaustion. Therefore such reports will be watched with concern by workers in this field.

In our series an occasional rise in blood sugar after stabilisation was invariably traced to dietary indiscretion and control was easily re-established by mere dietary control. We have not met with other causes of delayed failure.

As intercurrent infection is known to raise the insulin requirements of a patient, some workers advocate a switch back to insulin therapy during infection. In one of our patients the blood sugar rose during infection and remained high even after the patient was successfully treated with antibiotics for the infection (pneumonitis). We had to increase the dose of carbutamide in this case and the blood sugar gradually returned to normal. This was repeated twice in the same patient. We therefore feel that during episodes of infection therapy with sulphonylureas may be patiently continued and only if the infection is overwhelming, or if there is severe worsening of the diabetic state, indicated by ketosis, should insulin be administered.

Acknowledgments

We are thankful to the pathology department of this College for the co-operation in carrying out the liver function tests, blood cholesterol estimations, and the blood counts. We are grateful to the honorary physicians of the Sassoon Hospitals, Poona, for referring to us their diabetic patients, and to Hoechst Fedco Pharma Ltd. for the supply of 'Rastinon' brand of D-860, and to Boots Pure Drug Co. Ltd. for the supply of 'Bucrol' brand of BZ-55.

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ECTOPIA TESTIS TRANSVERSA

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Hertzler (1916) reported a case where both testes had descended into one side of the scrotal sac, and he reviewed 13 other cases reported earlier. No other case appears to have been reported after him in English literature, and most authors refer to him while discussing the subject. The condition is thus rare. A case of this anomaly under our treatment is reported.

CASE REPORT

A. K., a two-and-a-half-year old boy, was admitted to the L. L. R. Hospital, Kanpur on 10-7-59 complaining of a swelling in the left inguinoscrotal region for one year. There was no history of the swelling having been present since birth. The father stated that a swelling appeared in the scrotum when the child strained. He was not aware that the right side of the scrotum was empty.

General examination of the patient showed nothing abnormal. The child was of thin build. There were no signs of hormonal deficiency and the heart and lungs showed nothing abnormal. He was not anaemic, the haemoglobin value was 13 g. per cent, and the urine was found to be normal.

Local examination revealed a fullness in the left inguinoscrotal region. The right side of the scrotum was small and underdeveloped, and no testis could be felt on this side either in the scrotum or in the inguinal region. The left side contained a well-developed testis. Above the testicular swelling another small swelling appeared when the child coughed repeatedly. This was easily reducible, and the cough impulse was present in it.

Pre-operatively a diagnosis of an indirect inguinal hernia on the left side and an undescended testis on the right side was made.

Operation notes—The operation was performed on 14-7-59 under general anaesthesia. An incision two inches in length was made about half an inch above the inguinal ligament. The skin and superficial fascia were incised and the spermatic cord was exposed beyond the external inguinal ring. The coverings of the cord were then incised and the sac was exposed. The sac was thin and was dissected from other structures of the cord. During dissection a rent was produced in the sac through which a small quantity of thin clear fluid flowed out. The sac was of congenital type and had to be separated slowly. During separation of the sac a second testis was found lying at a slightly higher level. This testis was covered with its vaginal sac which appeared to be an outpouching of the vaginal sac of the other testis (Fig. 1). The vaginal sac was opened and the presence of testis inside it was cinfirmed. The inguinal canal was opened by incising the external oblique aponeurosis at this stage to facilitate dissection of the sac upto the internal ring and to study the spermatic cord. There were two spermatic cords lying side by side and were emerging from the internal inguinal ring. There were two separate vasa deferentia, spermatic arteries and pampiniform plexuses. After excision of the sac the two testes were placed in respective places and the coverings of the cord were stitched, the wound being closed in layers.

FIG. 1 SHOWING RELATIVE POSITIONS OF THE TWO TESTES AND THE TUNICA VAGINALIS

Post-operative progress—On the day following that of the operation, the patient had a marked swelling of the scrotum due to epididymo-orchitis and the temperature rose to 103°F. Tetracyn 50 mg. was given intramuscularly twice daily, and a scrotal support was provided. The temperature settled down in three days, but the swelling of the scrotum took much longer to subside. The stitches were removed on the eighth day after the operation. The patient was discharged on 27-7-59.

An intravenous pyelogram was taken before the patient was discharged from the hospital. It showed both the kidneys, ureters and the bladder to be normal in position and shape.

DISCUSSION

An ectopic testis is one which becomes aberrant in its descent and anchors at a point outside its normal course. Four varieties of ectopic testis are usually described, viz., (i) interstitial, when the testis passes upwards and laterally from the external inguinal ring towards the anterior superior iliac spine, (ii) penile, when the testis lies at the base of the dorsum of the penis, (iii) femoral, when the testis lies in the medial part of the femoral triangle, and (iv) perineal, when the testis lies in the perineum. A fifth type which is very rare is

the one in which both testes descend into one scrotal pouch. Lenhossak (1886) designated this condition as ectopia testis transversa. The condition is to be differentiated from polyorchism in which a supernumerary testis is found in addition to the two normally descended testes.

Theoretically there could be three possibilities when the two testes could be present on one side of the scrotum and none on the other side. Firstly, the two testes could develop from the genital ridge on one side, and none or only an atrophic testis on the other side. This condition would be similar to renal duplication in which two kidneys develop on one side and the kidney on the other side is atrophic or not developed at all. The condition is apparently very rare like its counterpart in the kidney. The case reported by Marsh (1911), quoted by Hertzler (1916) might belong to this category although Hertzler (*loc. cit.*) has reviewed the case as one of ectopia transversa. In this case two testes were found on the left side of the scrotum at operation. The child subsequently died and the post-mortem examination showed that there was only one vas deferens and only one seminal vesicle. The absence of vas deferens and seminal vesicle is in favour of the possibility that the testis also did not develop on that side.

The second possibility as to the cause of the two testes being on one side of the scrotum and none on the other is that two testes may develop on one side and descend into the homologous side of the scrotum. On the other side also a normal testis develops, but it fails to descend into the scrotum and gets retained in the abdomen. This condition should also be very rare and there appears to be no such case on record.

The third possibility is that of ectopia testis transversa, the condition in which the testes develop one on each side but due to some anomaly the testis of one side crosses over to the other side and both testes descend into one side of the scrotal sac. This condition is similar to the crossed renal ectopia. It is usually the testis of the right side which crosses over to the left, and the two testes descend into the left side of the scrotum. No apparent reason may be found for this crossing over ; however in some cases the anomaly can be explained on the basis of the findings at operation. For example, in the case reported by Hertzler (1916) and the one reported by Cornil and Brossard (1907), quoted by Hertzler (1916), a rudimentary uterus was found lying between the two testes and it was adherent to the epididymis of both sides. Evidently in these cases the Müllerian system had become adherent to the Wölffian body and the whole mass could descend only on one side, or not at all. In the case reported by Lenhossak (1886), quoted by Hertzler (1916), the two vas deferens were closely bound together with connective tissue for some distance beyond the internal inguinal ring. Here also the testes got so bound together that they had to descend on one side. In a case reported by Casteili (1909), quoted by Hertzler (1916), a fibromuscular band connected the testis lying in the inguinal canal with the other normally placed testis on the same side of the scrotum. Here it is quite possible that the fibromuscular band (possibly gubernaculum) was responsible for dragging the other testis into the opposite side of the scrotum.

At what level of descent the testis crosses over to the other side is another point worthy of consideration. From the fact that in some cases an infantile uterus was found entangled between the epididymis of the two sides, it appears that the crossing over occurs in the lower part of the abdomen. The course taken by the vas deferens of the crossed testis would be a valuable evidence on this point. Since most cases were such as were exposed at operation, a detailed study of the course taken by the vas deferens has not been reported in most cases. However, Berg (1904) quoted by Hertzler (1916), followed the course taken by the vas deferens in his case. In this case both testes had descended into the left side of the scrotum. At operation, the right vas deferens was found to be coursing across the space of Retzius from the right inguinal ring to the left inguinal ring. Thus the right testis had first descended normally up to the region of the right internal inguinal ring. From here it moved across the space of Retzius and reached the left internal inguinal ring to descend finally into the left side of the scrotum. He found the right inguinal ring to be completely closed.

Thus the course taken by the vas deferens indicates the level at which the crossing of the testis to the other side took place, and it also gives a definite evidence whether we are dealing with a case of duplication of the testis or with a crossed ectopia. It is not possible nor desirable to open the abdomen in these cases merely to follow the course of the vas deferens. However, if a skiagram could be taken after injection of a radio-opaque dye into the vas deferens of the crossed testis at the time of operation, its exact course could be determined.

In our own case reported here, there appears to be crossed ectopia of the right testis into the left scrotal sac. We did not open the abdomen and therefore the course taken by the right vas deferens will remain a matter of conjecture. We did not find any apparent cause for the descent of the right testis into the left side of the scrotum.

Summary and Conclusions

The case of a patient in whom both testes had descended into the left side of the scrotum is reported, and the literature reviewed. The term crossed ectopia testis appears to be more descriptive and accurate for this condition than the term ectopia testis transversa given by Lenhossak.

From a study of the reported cases it is pointed out that the crossing over of one of the testes to the other side occurs in the lower part of its descent. In some cases the Wölffian ducts got adherent to the Müllerian ducts, and in some others the two Wölffian ducts (vasa deferentia) got adherent to each other during the course of development. Under these circumstances the two testes could descend to one side only, or not at all. In one case the gubernaculum of the crossed testis was found to be attached to the normally placed testis. In many cases no cause of maldescent can be found.

It is suggested that the course of descent taken by the ectopic testis could be found out without opening the abdomen if a radio-opaque dye is injected into its vas deferens and a skiagram taken at the time of operation. This would also be important in establishing that crossed ectopia actually exists.

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PRACTITIONERS' SERIES

THE CURRENT STATUS OF SULPHONYLUREAS IN EXPERIMENTAL AND CLINICAL DIABETES

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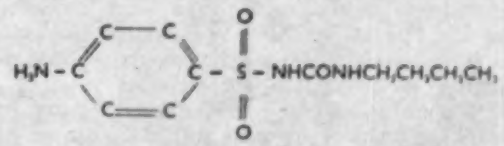
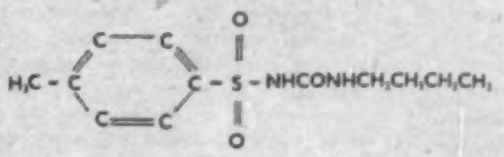
The discovery of the hypoglycaemic action of the sulphonylurea drugs is an excellent example of how a purely casual observation of the side-actions of a compound may lead to the discovery of drugs of clinical usefulness. In 1942 Janbon of the Medical School of Montepellier was investigating the potential usefulness of various compounds in typhoid fever and noticed that one drug, an isopropylthiodiazole derivative of sulphanilamide produced in some patients neurological symptoms that could be alleviated if glucose was given intravenously. He suspected that the drug produced hypoglycaemia and brought these observations to the attention of a colleague, A. Loubatieres, working in the same institution. Loubatieres had considerable experience in experimental diabetes and so was prepared to undertake a series of studies to uncover information on the mechanism of action of this drug. He found that the oral administration of the drug did, in fact, produce hypoglycaemia and although it did not have a direct effect on carbohydrate metabolism, it produced some metabolic changes similar to those of insulin. He also found that this action was absent in the completely depancreatised dog but if as little as 1/6 of the pancreas remained hypoglycaemia was produced. Similarly, the blood sugar in rabbits made diabetic by alloxan could be lowered by the oral administration of the drug provided some islet tissue was preserved. From these and other observations he concluded that the hypoglycaemia was due to the direct stimulation of the insulin-secreting cells of the pancreas.

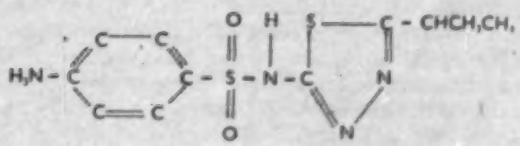
Because of the interest in finding oral hypoglycaemic agents useful in diabetes, the observations of Loubatieres stimulated investigations of the effects of this and many other derivatives of sulphonamide. Two types of compounds have been studied both in animals and in human diabetes ; the urea derivatives, of which carbutamide (BZ-55) and tolbutamide (Orinase) have been most extensively studied ; and the thiodiazole derivatives, of which the isopropylthiodiazole sulphonamide (3) was the initial compound investigated.



Carbutamide



Tolbutamide



Isopropylsulphathiodiazole

The principal structural difference to be noted between carbutamide and tolbutamide is the substitution of a CH_3 group for the NH_2 group on the benzene ring. This does not alter the hypoglycaemic activity but it appears to affect the toxicity as the side-reactions of carbutamide have led to its withdrawal from therapeutic use.

The result of more extensive work in other laboratories confirmed Loubatieres' observations that the sulphonylureas do control glycosuria and hypoglycaemia. These symptoms are two outstanding characteristics of diabetes and their control is generally recognised as an indication of effective insulin action. However it does not necessarily follow that substances that have hypoglycaemic actions will be useful in the management of diabetes. A major question is whether these compounds produce hypoglycaemia in a physiological manner presumably like insulin or by some unphysiological action. If the sulphonylureas exert their action chiefly by stimulating the secretion of insulin the hypoglycaemia should be accompanied by metabolic alterations associated with insulin hypoglycaemia.

There are a number of different ways in which alterations of metabolic processes may affect the blood sugar level and the quality of sugar in the urine. For instance, hypoglycaemia may result from a decreased liberation of glucose from the liver or an increase in the utilisation by the peripheral tissues. To determine by what mechanism these drugs were acting two principal approaches have been followed ; one that proposes these agents act on the liver inhibiting one or more enzyme systems involved in the formation and release of glucose ; the second, that the sulphonylureas and related compounds produce their effect by increasing the rate of formation or liberation of insulin, by potentiating or synergising its action or by inhibiting its destruction and excretion.

Despite the intensive work during the past few years the locus of action is still unknown, in fact the data from different laboratories indicate numerous sites of action. For example, there is evidence from animal experiments strongly suggesting that the drug stimulates the release of insulin by the β cells. There is equally strong evidence that some of the effects of these drugs are different from those observed following the parenteral administration of insulin. The reasons for such conflicting data are difficult to determine. An important factor overlooked is that most pharmacological substances (even naturally occurring physiological ones) are not characterised by one exclusive mechanism of action. Generally an agent has a principal action and a number of secondary ones. Both the principal and secondary effects depend on many factors ; which one may dominate is often determined by the experimental conditions and species. Another possibility is that endogenous insulin released by the sulphonylureas may not have the same effects as exogenous insulin, which is injected into the peripheral circulation. (It is too frequently overlooked that endogenous insulin is released into the liver *via* the portal vein and this may have an important influence on its subsequent action).

Finally, a major difficulty in assessing the results is that different investigators have been using different doses, routes of administration and studying different metabolic responses.

Nature of the Hypoglycaemic Response

In healthy animals and men tolbutamide produces a hypoglycaemic response characterised by 2 phases. The initial phase, lasting one hour resembles the effect produced by insulin, in which a maximum decrease in blood sugar occurs. The second phase is of variable length and characterised by a gradual restoration of the blood sugar to normal. With small doses of tolbutamide (50 mg./kg. or less) the response in both phases is dependant on the dosage. For instance, with 10 mg./kg. the maximum lowering of blood sugar is about 70 per cent of normal ; with 20 mg./kg. about 60 per cent of normal. With doses larger than 50 mg./kg. the maximum lowering of the blood sugar during the initial phase is not further increased, but the second phase (the 'restitution phase') is prolonged. According to Mirsky the initial phase is due to the direct stimulation of the β cells and the discharge of insulin from the pancreas into the circulation. The prolonged restitution phase is due to the action of tolbutamide in inhibiting insulinase and as a conseuence a decrease in the rate of destruction of circulating insulin.

Effects of Sulphonylureas on the Pancreas

As pointed out above, Loubatieres reported that the presence of the pancreas, or at least 1/6 of it, was required for the hypoglycaemic action of these drugs. This was confirmed by other investigators. Houssay also noted that convulsions and coma were more easily produced in adrenalectomised animals and these toxic symptoms could be prevented by the sufficient administration of glucose.

The daily administration of carbutamide or tolbutamide in dosages sufficient to induce a significant hypoglycaemia in rabbits produces a mild and sporadic degranulation of the β cells during the first 3 days. After the 4th day the degranula-

tion is well marked and by the 8th day (in some animals) almost a complete loss of β cells is seen. These observations suggest that these compounds stimulate the β cells of the pancreas to increase insulin output and this is reflected by morphological changes. However, it must be remembered that although β cell degranulation correlates with insulin content it is not necessarily a measure of insulin formation or release. These studies do not, of course, exclude extra-pancreatic actions.

The Effects on Insulinase Activity

The results from different laboratories are conflicting. It was already noted above that there is some evidence that the destruction of insulin is retarded by these drugs. However Volk *et al*, and Wick *et al*, report that the metabolic degradation of insulin labelled with I^{131} is not altered by tolbutamide and both groups of investigators conclude that it is unlikely that the hypoglycaemic action is due to an inhibition of insulinase. However Mirsky found that the insulinase activity of a fresh extract of livers of rats one hour after they were given tolbutamide (100 mg./kg.) by gavage was significantly lower. It might well be that the conflicting results are due to different assay procedures. Furthermore there are reports of 2 factors in the enzyme insulinase, a heat-labile factor, sensitive to the sulphonylureas, and a heat-stable factor, which de-iodinates the I^{131} insulin and which is unaffected by these drugs.

Hepatic and Miscellaneous Effects of the Sulphonylureas

There is an abundance of evidence indicating that these agents have in addition to their pancreatic action, other actions not accountable by increased insulin output. Glucose production by the liver is inhibited by tolbutamide. The incorporation of C^{14} into amino acids is also increased. There are reports of qualitative as well as quantitative differences between the actions of tolbutamide and insulin on liver and muscle glycogen and potassium, as well as the incorporation of C^{14} glucose into liver and peripheral fat. Plasma insulin activity is not increased after tolbutamide. Sulphonylurea, unlike insulin, does not increase the distribution in the body of xylose.

Clinical Experience with the Sulphonylureas

There are some conflicting data from different clinics but evidence to date indicates that the sulphonylureas can and do control glycosuria and hypoglycaemia in the maturity-onset type of diabetes. The frequency of success averages about 70 per cent. The side-reactions encountered with carbutamide have led to its withdrawal from therapeutic use. Tolbutamide shows fewer and milder toxic reactions when the average daily dose lies between 1 and 1½ g. with a maximum set at 2 g. per day.

Dolger reported on 500 patients treated with tolbutamide for a period of one year. Most of these patients were over 40 years of age and over 300 showed an excellent response to treatment with the drug. He reported that only the age of onset of diabetes or previous history of coma influenced the result. According to him, sex, weight, prior insulin requirement, duration of insulin therapy and history of ketosis were without influence on the eventual response to tolbutamide. He did not note a single serious toxic effect in the entire group treated over the one year period. Stotter *et al*, of the Medical Clinic of Ausburg, also report great relief with the oral administration of tolbutamide in the older diabetic. These clinicians, however, combined their therapy with strict dietary treatment.

Doctor Sugar of George Washington University reported on 143 diabetics treated with tolbutamide for 2 or more months. Approximately 76 per cent showed adequate control (average blood sugar less than 200 mg. per cent, daily excretion of glucose below 15 g.). Of the 34 failures 10 were juvenile type diabetics requiring relatively large doses of insulin and with a pronounced tendency to ketosis. Of several patients with ketosis only one responded favourably on tolbutamide. In general, he reported, the most easily controlled patients were the middle aged with a relatively recent onset of diabetes and requiring less than 40 units of insulin, while the unstable diabetic of any age were difficult to manage with tolbutamide. In his patients who were controlled by insulin he shifted them to tolbutamide 24 hours after the last dose of insulin. After an initial loading dose of 2·5 g. he followed with 1·5 g. 24 hours later and then a maintenance dose of 1 g. every morning thereafter. If control was still difficult he increased the dose. Diet was also maintained at optional caloric requirements and frequent qualitative tests for urine sugar and acetone were made.

There is general agreement among clinicians, experienced with these drugs, that it is imperative that those treated observe the same dietary control as is employed for insulin therapy. It has also been demonstrated that any complication, such as infection, etc., may require the temporary use of insulin ; therefore the instructions to patients in the use of insulin must never be neglected.

A SHORT HISTORY OF THE DEVELOPMENT AND PROGRESS OF RESEARCH ON BIOLOGICAL CONTRACEPTIVES

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One of the urgent problems facing the modern world is the rapid growth of population in almost all countries. To make matters worse, the problem of overpopulation is most acute in underdeveloped countries, and India, in particular, is facing a crisis of perennial food shortage. Every country is trying to maintain and improve upon the existing standard of living. There is but one way to achieve this, without unduly depleting the natural resources and reserves of the earth, that is by the introduction of a safe, reliable and reasonably cheap oral contraceptive for checking the rising birth-rate.

Dr. Conant, Director, Harvard University, and now a Director Emeritus, had remarked that the future of the world was rather gloomy, on account of the rapid increase in the growth of population all the world over and that unless and until a cheap and harmless oral contraceptive could be developed, population growth could never be checked on a world-wide scale. He also remarked at the same time that he was afraid that it would take another hundred years to develop such a contraceptive. Unfortunately, Dr. Conant was not aware of the fact that such an oral contraceptive had already been developed in India (Sanyal, 1949), where the problem is most acute, from an edible cereal, viz., the common field pea, in 1949. By the time, he gave out his warning, the active principle of the oil of *Pisum sativum* had already been isolated and synthesised (Sanyal, 1952). This synthetic active principle is proved to be m-xylohydroquinone. The maiden trial on human subjects with this oral contraceptive was instituted in 1953 and was completed in 1955 (Sanyal and Ghosh, 1955).

Knowledge Already Existing

It is well known that extracts of female and male sex glands are antagonistic to each other. Injection of oestrogen into immature male rats for 30 days caused atrophy of the testes and accessory genital organs (Moore and Price, 1930). This acted by diminishing or arresting the output of gonadotrophin FRH from the pituitary. Testosterone propionate given to mice was followed by failure of implantation or decrease of spermatogenesis (Burdick, *et al*, 1940).

Effect of Excess of Gonadal Hormone

When given in small doses for a short period, the gonadotrophic activity of the pituitary increased but large doses or prolonged administration suppressed it (Frank, 1940). Oestrogen injected early in the cycle may inhibit follicular development (Sturgis and Albright, 1940). Pregnanediol which is a metabolic product of progesterone, found in the urine, appears to be antiprogesterone in activity (Hisaw and Velardo, 1951). Diethylstilboestrol or ethenyl oestradiol, given orally, can interfere with gestation by inhibition of the luteal phase of the cycle (Parkes, 1938). Progesterone, by various routes, has been reported to cause alteration of the normal cyclic processes in the rabbit (Boyarsky *et al*, 1947), rat (Astwood and Fevold, 1939), heifer and also in the human (Parkes and Rowlands, 1936). It is also known that repeated injections of testosterone propionate in the male reduce the number of spermatozoa in the semen and might even reduce it to zero (Hackel and MacDonald, 1952). When discontinued, the sperm count reverts to the original or even to higher values.

The literature on the subject is voluminous. In spite of the existing knowledge on the subject, the top-ranking scientists and biologists were not specifically interested in the research for oral contraceptives. Instead, their researches were directed towards the introduction of suitable hormones as correctives, to be administered for short periods only. They did not advocate the use of hormones for producing contraceptive effect, where prolonged administrations were required for months and years. This was because of the apprehension of probable hormonic imbalance in the system. Persistent prevention of ovulation might be reflected in the breakdown of the pituitary control in some cases. Besides, these hormones are the most potent biological substances and the sex apparatus is also a very delicate one. Further, cholesterol forms the basis of steroid hormones and also of the carcinogens.

Apart from steroid hormones the effect of an African herb, gromwell (*Lithosperma rudarale*, a desert tea-herb) was known to scientists. Cranston (1945) detected the inhibition of gonadotrophic activity of *Lithosperma rudarale*. He studied its effect on the oestrus cycle of mice. At 20 to 40 per cent level in the diet, there was reduction in the body weight and a greater proportionate reduction in the weight of the sex organs. There was also complete cessation of the reproductive cycle.

In the Haskins Laboratory Drasher and Zahl (1946) detected its effect on the oestrus cycle of

mice and also observed that LH was also affected (Zahl, 1948). They further observed that life-expectancy of mice was reduced from 17 to 13½ months by continual feeding at 10 to 20 per cent level (Cranston and Robinson, 1949).

Indigenous Methods

The idea of the use of contraceptives is not of recent origin but existed from the time immemorial. Even in ancient China, there was a belief as stated by the herbalist deputy, Yeh Hai Chun, that if 14 living tadpoles are swallowed 4 days after menstruation and the next day 10 tadpoles, there would be no conception for 5 years. If this process is repeated twice consecutively, the female should be sterile for good. This was discussed by Shoo Li Tzu in a lecture delivered before the First National Peoples Congress, Peking, on 20th of June, 1956.

After the publication of the preliminary note on the sterility effect of *Pisum sativum*, a laboratory was started in the U.K. with M. deLaszlo as director. About 60 varieties of herbs were collected from different parts of the world (Hensaw and deLaszlo, 1954). After screening, about six of them were found to have some contraceptive effect. Unfortunately nothing positive came out as a result of these investigations.

Pisum sativum Linn

In India, widows are enjoined to a restricted diet containing amongst other things, common field pea (ripe, dried and husked, called *Matar dal*) perhaps with the idea of inhibiting the sex urge. Nag and Pyne (1935-36) while determining the vitamin content of different cereals, by feeding experiments on rats, discovered that rats, fed on *Pisum sativum* alone, did not produce litter. This was true both for males and females. This was supposed to be due to want of vitamin E in the seeds. The authors' contention was that this might be due to the presence of some anti-vitamin E in the seeds. Numerous experiments were conducted on rats, both immature and mature (Sanyal, 1950) and also ovariectomised (Sanyal, 1951), and it was found that the oil of the seeds, its active principle and also the synthetic active principle (Sanyal, 1952), prevented or reduced litter-formation by interferring with the action of gonadotrophin and progesterone. Noble and Graham (1956) tested the effect of oil of *Pisum sativum* and also the synthetic active principle, m-xylohydroquinone and found its anti-gonadotrophic effect in smaller doses and none in higher doses. Rosen and Millman (1955) tested the anti-gonadotrophic activity of many quinones and related compounds and in their opinion, 2 : 6-dimethylhydroquinone was as active as many such compounds. Their method of testing was to mix this compound with pregnant mare's serum and inject the mixture to rats where oestrus cycle was found to be prevented. This was found effective by parenteral route but not so when given orally. Significant effect lasted for 7-12 days despite repeated injections. Beiler *et al* (1953) conducted experiments by feeding these seeds to rats. Their observations were that at 20 per cent level, litter-formation was much reduced and at 30 per cent level it was abolished. Pincus (1956) observed that m-xylohydroquinone interfered with fertility by inhibiting gonadotrophic activity. Human trial was conducted with this oral contraceptive by the author in collaboration with Dr. Mrs. S. Ghosh of Baldeodas Maternity Hospital, Calcutta (Sanyal and Ghosh, 1955). This trial with oral contraceptive on human subjects was the first of its kind. The Government of India conducted a second trial, under the aegis of the All-India Institute of Hygiene and Public Health, Calcutta (Chandrasekharan, 1959), and endorsed all the findings of our first trial. The administration of the drug was only twice every month and the cost of a single dose is negligible (less than that of an aspirin tablet). It has no toxic effect is not an abortifacient, causes no permanent sterility and produces no deleterious effect in the child in failure cases (Sanyal, 1956).

This oral contraceptive, m-xylohydroquinone, has been found to be effective in cases of males also. Animal experiments on rats (Sanyal, 1958), so far conducted, produced clear evidence that by inhibition of gonadotrophin, spermatogenesis could be reduced. Human trial (Sanyal and Rana, 1959) is also being conducted and the results so far obtained, are encouraging.

Lithosperma rudarale

Investigations with lithosperma were undertaken by different groups of scientists. Drasher (1950) studied the inhibition of luteinising hormone of the pituitary by lithosperma. He also found it to be effective when injected, but not so when given orally. Variations were detected in different samples as regards their effect on either FRH or LH. Root extracts antagonised LH only. There was also found some oestrogenic principle which clouded the main action to some degree. Another hormone which connected pituitary action with thyroid (thyrotropic) also appeared to be antagonised (Plunkett *et al*, 1950 ; Noble *et al*, 1950). Seasonal variation as regards anti-gonadotrophic action of lithosperma (Noble *et al*, 1950) was studied by Graham and Noble (1952).

Wiesner and Yudkin (1952) studied inhibition of oestrus by cultivated gromwell.

Blocking of pituitary hormone with lithosperma was studied by Kemper and Loeser (1958a) and also the regulation of pituitary hormone production by lithosperma. Blocking of hypophyseal gonadotrophin, thyrotrophin, chorionic gonadotrophin, pregnant mare serum and prolactin, in rats and guinea-pigs, in their opinion, was of the nature of inactivation which occurred after secretion from the gland. Inactivation occurs after incubation with the respective hormones and there was no direct action on the pituitary. When lithosperma extract was injected into rats, their pituitaries were found to contain normal gonadotrophin and thyrotrophin hormones. In a second series (Kemper and Loeser, 1958b), rats were treated with 50 mg of $NaIO_4$ for 11 days, enlargement and increase in weight of the thyroid was noticed. Subsequently, when these were injected along with 100 mg. of lithosperma extract, there was no increase in weight of the thyroid. Their conclusion was that the drug did not inhibit hormone synthesis but the peripheral action was blocked after release. Inactivation of gonadotrophin by lithosperma is not the same as by periodic acid and the extract contains a substance, removable by dialysis (English and Noble, 1953), which interferes with the inactivating principle.

Unfortunately its active principle could not be isolated as yet. According to some authorities this is perhaps made up of some complex tannin-like substances which combine with the luteinising hormone, which is believed to be a protein of low molecular weight (Skelton and Grant, 1951), and the resulting flocculated jelly-like product was unable to penetrate through the different membranes including those in the target organs for the hormones. Other effects were also studied by Zahl and Novak (1951) as regards the incidence of spontaneous mammary tumours in mice with lithosperma-induced dioestrus.

Anti-hyaluronidase

A substance was isolated from orange peel by Alexander Sieve which was found to be antagonistic to hyaluronidase an enzyme normally present in semen and in the spermatozoa. With this compound, phosphorylated hesperidine, he claimed to have tried on human females with 100 per cent success. In a subsequeent trial the result could not be repeated. However this may be effective locally when applied in the form of a jelly.

Studies with Clover

It was already known that sheep fed on clover, become sterile. Studies in this direction determined that subterranean clover (*Trifolium subterraneum*) induces constant oestrus (Bennette and Underwood, 1949 ; Robinson, 1949 ; East, 1952), when fed to ewes. The active agents seemed to be isoflavones (Bradbury and White, 1951, 1953). Similar materials have been isolated from soya-bean derivatives (Cheng *et al*, 1953). This effect might also be due to *cumestrol* (a *furocoumarin*) which is oestrogenic in activity. Oestrogenic activity of cumestrol was studied by many scientists (Bickoff *et al*, 1957).

Antihormone

Collip and Anderson (1935) first observed that animals treated with pituitary extract became refractile after an initial period of stimulations. Serum from refractory animals inhibited the action of hormone administered to untreated animals. Antihormone does not form spontaneously and could not be demonstrated in untreated individuals and does not form when the donor of the hormone and the recipient are of the same species. It may possibly be transmitted and is similar to if not identical with antibody. Formation of antihormone is often delayed after first week and usually appears after the second or third week and lasts for a limited but undetermined variable period. Allergy might result during subsequent treatment. Antihormone does not destroy but irreversibly combines with or prevent production or release of pituitary gonadotrophin. Antihormone formation in patients receiving gonadotrophin therapy was also studied by Maddock *et al* (1953 and 1956). The practicability of this as an antifertility agent remains questionable.

Another biological method was tried by producing a special form of allergy to testicular tissue which would prevent the development and passage of spermatozoa. Here the other organs were not affected. A non-protein compound was isolated from the testicular extract (Freund *et al*, 1935) and this was found responsible for aspermatogenesis, anaphylaxis and cutaneous sensitisation.

Change in the condition of the Cervical Secretion

Contraceptive effect is possible by changing the condition of the cervical secretion and thus preventing the passage of spermatozoa through the cervix. During oestrus the cervical secretion is thin and watery and the condition is such that during their passage the spermatozoa are not agglutinated while at other times the secretion is rather mucoid and at the same time agglutinates the spermatozoa. This antagglutinin factor was studied by different workers. (Lindahl and

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Kehistrom, 1956 ; Wilson, 1956). This factor was found to be allied to but not identical with vitamin E.

Antihistaminic Agents

Antihistamines block the development of decidual cell reaction, both artificially induced and naturally associated with nidation (Shelesnayk, 1956). Histamine, in massive doses, introduced intravenously or intraperitoneally, provokes the endometrium to decidual cell response (Shelesnayk, 1959). Intrauterine antihistamine suppresses the systemically induced decidual cell reaction (Kraicer and Shelesnayk, 1958). When introduced intraluminally antihistamine might inhibit natural ovum implantation in the impregnated rat. A prenidation infiltration of uterine tissue with polymorphonuclear leucocytes and eosinophils and presence of mast cells suggest an accumulation of histamine sources, and disappearance of these cells during implantation, suggests release of histamine. This framework points out the possibility for fertility control by interfering with nidation through the action of antihistamines (Shelesnayak and Johnson, 1958).

Steroid Hormones

As stated before, male and female sex hormones are antagonistic to each other. Also, excess of the gonadal hormone prevents ovulation in the female and spermatogenesis in the male, through the inhibition of the gonadotrophic hormone of the pituitary and in this way might produce contraceptive effect. These steroid hormones have been synthesised from cholesterol and many analogous new steroids have been developed and styled as antimetabolites (Rock *et al*, 1956). Steroid hormones are so closely allied that small changes in their configuration, without introducing any drastic change in the molecule, bring about far-reaching changes in their activity. Δ-1-androstenedione is oestrogenic but Δ-4-androstenedione is androgenic, whereas Δ-5-androstene-3-17-diol is both oestrogenic and androgenic (Butenandt, 1936 ; Burrows, 1949).

The American authorities reopened the use of steroid hormones for contraceptive effect. With excess of progesterone ovulation could be cut off (Slechta *et al*, 1954). Greenblatt (1956) studied the progestinal activity of norethisterone. The effect of certain norsteroids on reproduction in animals was studied by a group of scientists (Pincus *et al*, 1956). Rothschild (1957) studied the effect of large doses of intravenous progesterone on the gonadotrophic excretion in the human females. Physiologically inactive analogue of progesterone may have the capacity to compete with or replace progesterone to a greater or lesser degree in the sequence of events which occur in the endometrium. Thus it might be possible to prevent the development and/or maintenance of a secretory state and so interfere with nidation of the embryo (Velardo *et al*, 1956). Progesterone is in reality a pregnancy hormone (Davis and Plotz, 1957). Effects of certain synthetic anabolic steroids in human subjects were also studied (Sachs *et al*, 1956). Another group of scientists (Rock *et al*, 1956) studied the effect of certain norsteroids on human menstrual cycle.

Of the many such synthetic steroids developed, the following were studied in detail :

(1) 17-1-methyl-19-nortestosterone (neosterone)
(2) 17-α-ethynyl-19-nortestosterone (norlutin or norethysterone)
(3) 17-α-ethyl-19-nortestosterone (nilevar)
(4) 17-α-ethynyl-1-5 (10) estraen-17β-ol-3-one (enovid)

These compounds are progestinal in action and some of them, as in the case of nortestosterone series, are also androgenic. The methyl and ethyl derivatives are also anabolic. Enovid combines in itself both progestational and oestrogenic activities. These compounds prevented conception in rats while treatment was continued and pregnancy resumed on discontinuation of the drug (Drill, 1959). In animals the weight of the gonads and accessory glands was reduced which was restored on discontinuing the treatment. Subsequently these synthetic steroid hormones were extensively tried on Puerto-Rican females and a success of 100 per cent was achieved. One of them enovid has already been marketed as a tablet. The cost of each tablet is 54 cents and it has to be administered for 20 days in the cycle. The cost is thus prohibitive. Besides, in spite of the tremendous success, as claimed by many authorities, these preparations would not solve the population problem, because of the undesirable side-effects, such as nausea, vomiting, headache, giddiness and most particularly the breakthrough bleeding and in some cases a lack of therapeutic effectiveness on continued therapy. During the administration of these steriods constant medical supervision is necessary. Further, these drugs are not excreted in the same manner in the urine as progesterone. It seems that the body might be storing some of the metabolic products in an out-of-the-way depot in a manner which may cause occasional difficulties after some years of use (Meier, 1959).

These steroids were also studied by Nelson (1959) on males. Two compounds, 17-1-methyl-19 nortestosterone and 17-α-ethyl-19-nortestosterone

inhibited spermatogenesis very little, although there was found sufficient reduction in the gonadotrophin content of the animal's pituitary. This suggested that perhaps the compounds had some direct stimulating effect on the seminal epithelium of the testes. In human experiment with all the above 19-nor-compounds and 3-methylether of ethynyl oestradiol, sperm counts were found reduced approximately to azoospermic level and on discontinuance they reverted to normal level, although in most cases, inhibition of Leydig cell function and consequent inhibition of libido of the patients, due to treatment, were observed.

Other Compounds Used for Specific Clinical Conditions

Interest for researches on oral contraceptives gradually extended and attempts were made to utilise recently introduced synthetic compounds and herbal derivatives. Hypotensive preparations, tranquillisers and halucinogen drugs were tried as possible oral contraceptives. Modification of the menstrual cycle in rhesus monkeys was noted with reserpine (DeFeo and Reynolds, 1956). Blockage of the release of the pituitary gonadotrophin by chlorpromazine was also studied (Barraclough, 1956). Furadantin, a nitrofurane derivative, used as urinary antiseptic has been observed to reduce spermatogenesis in man (Nelson and Bunge, 1957 ; Nelson and Steinberger, 1954 ; Featherstone *et al*, 1954 ; Paul *et al*, 1953). This was found ineffective in therapeutic doses. In higher doses the desired result was obtained but it was found toxic. Pyruvate oxidation in testicular tissue (Featherstone *et al*, 1955), during furadoxyl-induced arrest, was also studied. Nitrofurazone (Nissim, 1957) was found to possess antigonadotrophic effect. This caused degeneration of the seminiferous tubules and the prostate.

Alkylating Agents or Antileukaemic Agents

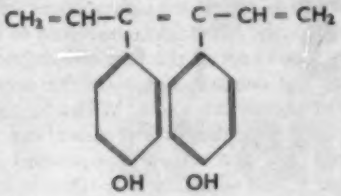
Like iodoacetate or iodoacetamide, alkylating agents, such as nitrogen mustard or sulphur mustard, also attack sulphhydryl groups and suppress mitosis (Barron, 1953). These are belived to be fixed by nucleic acid, the purines and pyrimidines and the irreversible reaction causes chromosomal malfunction (Skipper, 1953). The alkylating agents, so far tested for any contraceptive or abortifacient effect, are azaserine, (p-diazo-acetyl-l-serine), norleucine, aminopterin, 6-mercaptopurine, DON (6-diazo-5-oxo-norleucine), whose effects are counteracted by adenine, TEPA (N, N, N, triethylene phosphoramide), TEM (2,4,6-triethylene-imino-s-triazine or triethylene melamine), thioguanine, chlorambucile, desacetyl thio- or desacetyl-methyl colchicine, podophyllin and podophyllotoxin, etc. These compounds were tested for producing contraceptive effect or abortifacient effect usually by the destruction of the germ cells (Thiersch, 1952 ; 1954 ; 1957). TEM did not completely destroy the litter. It affected the placenta as much as the litter. In the case of TEPA, deformities were noted mainly in the head and face of the foetus and deterioration of the bone marrow and epithelial coverings of the mother was also observed. Folic acid antagonist, such as 4-amino or 4-methyl PGA, was effective in inducing abortion and caused no permanent effect on the mother. In this case the foetus was destroyed rather than the placenta. But there was risk of accumulation in the body attended with other ill effects in the long run (Thiersh, 1956). At the same time there is possible risk of malformation in the failure cases. TEM, when injected intraperitoneally, produced selective activity on the fertility of male rats where its effect was found reversible. This acted directly on the seminal epithelium (Bock and Jackson, 1957). β-acetylacrylic acid (Matz and Lagervall, 1958), was injected into pregnant mice, 0·3 mg. every 2nd day until 3 to 5 injections had been given and the mice were examined on the 16th day. It was noted that the controls had fewer atrophied embroys than the treated ones, but the total number of embroys in the two groups were the same.

Modern Trend

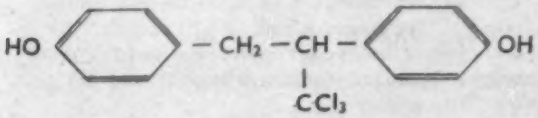
The recent trend seems to be directed towards the development of synthetic non-steroid compounds which may prove to be effective as contraceptives. Plant products did not come up to expectation sufficiently except m-xylohydroquinone, developed from the common field pea as already noted. Steroid hormones do not find approval from scientists and demographers. Attention is therefore directed towards simpler compounds synthetically produced.

Diethyl stilboestrol (diethyl stilbene dihydroxide) is the best example of this series of nonsteroid synthetic chemicals (Dodds *et al*, 1938). It has strong oestrogenic activity and is commonly used. It can produce contraceptive effect by excess in the supply of oestrogen. Two more synthetic compounds (Dodds *et al*, 1953) were developed, viz., 3-4-diparaoxyphenyl-hexa-1, 3, 5, triene which is approximately equal to diethylstilboestrol in activity and 1, 2-bisparaoxyphenyl-1-1-1-trichlorethane which is about seven times as active as its nonhalogenated congener. Oestrogenic action of DDT analogues were developeed by a group of scientists (Fisher *et al*, 1952). DDT or

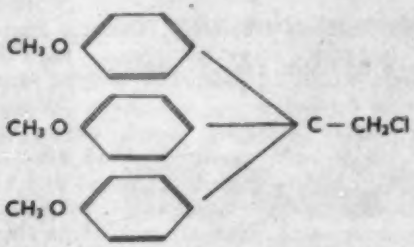
its analogue 1, 2-bis-paramethoxyphenyl-1, 1, 1, trichlorethane did not produce oestrogenic effect



even in 45 mg. doses but 1, 2, bis-paraoxyphenyl, 1, 1, 1-trichlormethyl ethane was found 7 times

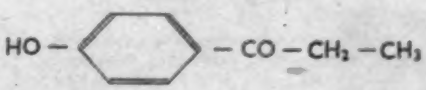


as active as oestrogen. This compound was also produced by Dodds and others and the same effect was also observed by them. Another compound (Rothchild and Keys, 1952) was produced, p-trianisylchlorethane (TACE), possessing oestrogenic



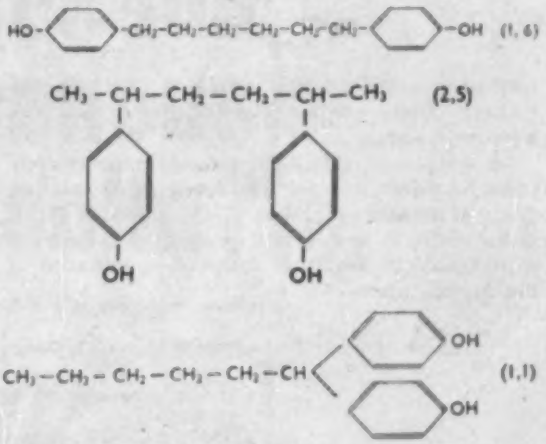
properties and found useful in menopausal females. In case of TACE, p-trianisylchlorethane, it was observed that 24 mg. in a single dose was not so effective as in 4 divided doses on 4 successive days. 48 mg. in 4 divided doses was found even more effective.

P-hydroxypropiophenone was developed (Rausher and Rennhofer, 1953) and tested. It was

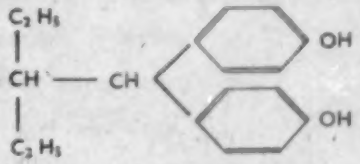


found to inhibit the gonadotrophin secretion (Desclaux *et al*, 1953) in rats producing temporary inhibition of sexual activity, regressive structural changes in genital organs and post-castration changes in the pituitary.

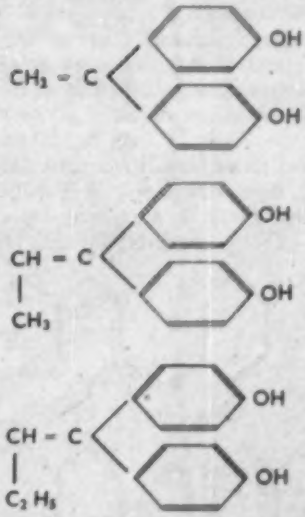
Several other compounds were synthesised by Scandinavian scientists (Miquel *et al*, 1952). The intravaginal applications of these drugs, related to oestrogen, could produce interference with oestrus reactions. These are, 1 : 6 ; 2 : 5 ; 1 : 1 ; bis-para-oxyphenylhexane



and 1 : 1-bis-para-oxyphenyl-2 : 2-diethylethane



also 1 : 1, bis-paraoxyphenylethylene or its 2-ethyl derivatives.

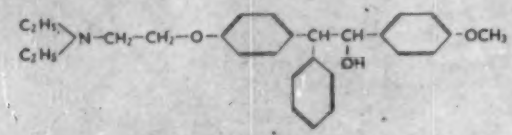


These compounds prevented the appearance of oestrus in spayed mice and rats, and may be used as hormone antagonists.

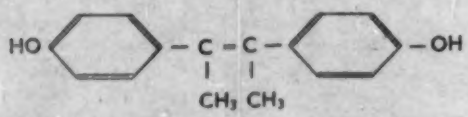
Another compound, 2-amino-5-nitro thiazole was found effective on males (Levis, 1957). 0·1 per cent of this compound in the feed delayed

spermatogenesis and age at sex maturity in the turkey. There was no residual effect. Chickens were more sensitive.

A compound, (MER-25) p-diethylaminoethoxyphenyl-2-p-anisylethanol was developed by another group of scientists (Segal and Nelson, 1958). When given orally to female rats on the day of mating, it prevented implantation, followed by initiation of the normal cycle.

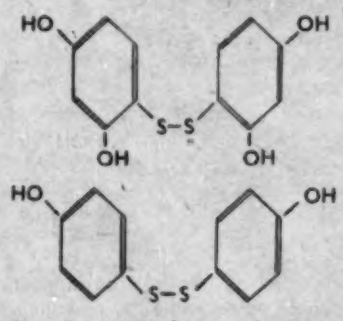


Diethyl stilboestrol (Emmens and Cox, 1958, 1959) was tested and was found to be an oestrogen inhibitor.



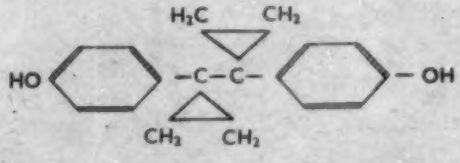
This compound inhibited vaginal smear response in spayed mice to oestradiol and diethyl stilboestrol if both of them were given simultaneously and intravaginally for two days. This had no effect if given separately or by other routes. In doses of 0·02 γ to 0·2 γ with oestrogen and 2 γ with diethylstilboestrol this was an oestrogen inhibitor but in doses of 50 γ it acted as pro-oestrogen.

Diphenylsulphide or diphenyldisulphide compounds had been developed in Japan (Shunyo, 1959). These are 2:4 dihydroxy-diphenyl-disulphide and 4: 4 hydroxy-diphenyl-disulphide.



In normal and castrated rats these preparations showed no androgenic effect but increased the weight of levator ani muscles. This action is shown by diethylstilboestrol but not by oestradiol-3 benzoate. The action is therefore independent of androgenic or oestrogenic effect. Administered to ovariectomised rats, the effect of the first one did not differ from that of the control, but with the second one the weight of uterus increased. While injected into males, the first one did not produce any change in the testes, but the second one caused atrophy of the testes. This suggests that these compounds are synthetic oestrogen differing in biological activity. Hydroxy groups increased the activity in comparison with other substitutions such as Cl, Br, I, nitro, COOH, CH_3.

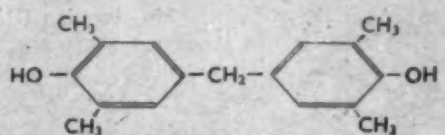
Cyclopropyl analogues of hexestrol and diethylstilboestrol were developed, for example, 1, 2 diparaoxyphenyl dicyclopropylethane and 1, 2 dicyclopropyl diparaanisylethane (Bennett and Bunce, 1960). The former is



In the author's laboratory, Calcutta Bacteriological Institute, many compounds have been synthesised which are related to m-xylohydroquinone or its derivatives and congeners. In the beginning, esters such as, acetyl, benzoyl, etc. (Sanyal, 1953), were prepared. And compounds like 2, 6-diethylhydroquinone (Sanyal and Guha Sircar, 1956 ; Sanyal, 1957) and 2 : 6 dimethylphenoxyacetic acid (Sanyal and Guha Sircar, 1957 ; Sanyal, 1957*b*) were prepared and tested by animal experiments.

Recently, instead of diphenyl compounds, dixylyl compounds have been prepared of which mention may be made of the following :

DIXYLYLHYDROQUINONE (4 :4'-DIOXY-3 :5, 3' :5'-TETRAMETHYL-DIPHENYL) COMPOUND (SANYAL AND GUHA SIRCAR, 1959 ; SANYAL, 1960)



2 :6-DIXYLENOLMETHANE (4 :4'-DIOXY, 3 :5, 3' :5' TETRAMETHYL DIPHENYL METHANE).

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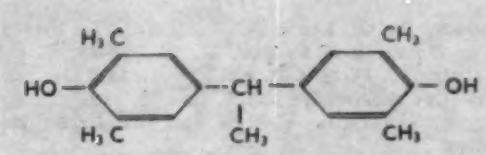
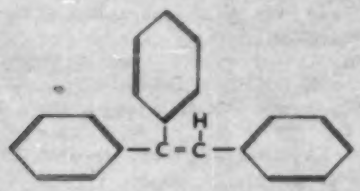
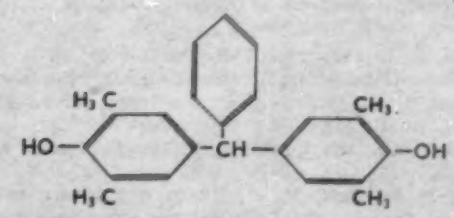


2:6 DIXYLENOLETHANE (4:4'-DIOXY-3:5, 3':5'-TETRAMETHYL-DIPHENYLETHANE)

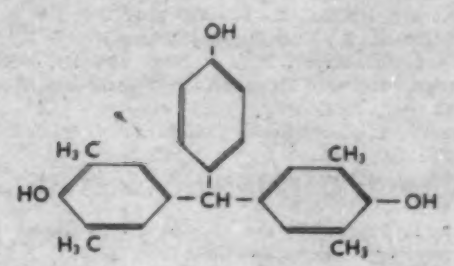
Triphenyl compounds had also been prepared long before and triphenylethylene was used as a



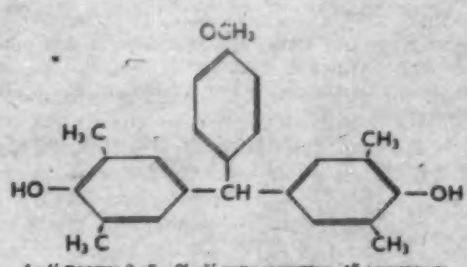
synthetic oestrogen. Three such compounds have also been developed in this laboratory:



4:4'-DIOXY-3:5, 3':5'-TETRAMETHYL-TRIPHENYL-METHANE.

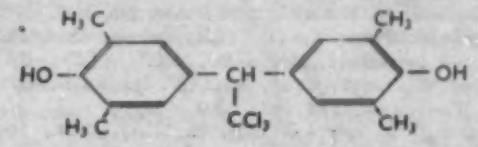


4:4'-DIOXY-3:5, 3':5'-TETRAMETHYL-4"-HYDROXY-TRIPHENYLMETHANE.



4:4'-DIOXY-3:5, 3':5'-TETRAMETHYL-4"-METHOXY-TRIPHENYLMETHANE.

A chloro-compound has also been developed—



4:4'-DIOXY-3:5, 3':5'-TETRAMETHYL-TRICHLORETHANE.

Dixylylhydroquinone and 2:6-dixylenolmethane have already been tested for their biological activity with encouraging results as regards their antigonadotrophic, antiprogestinic and antioestrogenic effects. Other compounds are intended to be tested for their biological activities as well as their toxicity in the near future. These compounds are simple and easy to prepare and the yields are satisfactory. These compounds are very stable and cheap at the same time. Human trial with these new compounds have not yet beeen undertaken.

No doubt, the perfect oral contraceptive is yet to come. The problem is now being tackled by renowned scientists all over the world. Various avenues of approach are being explored, especially in the field of chemotherapy. The development of an oral contraceptive, cheap and harmless, will not only solve the great problem facing the present world but will, almost certainly, be of immense benefit to the generations yet unborn, by ensuring lasting peace and prosperity on earth.

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GERIATRICS: ITS NEED IN INDIA

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Geriatrics, a newcomer in the field of specialities, has already established its need in countries where people live a comparatively long life. But in underdeveloped countries where the expectation of life is still low, geriatrics as a separate discipline has not got any footing as yet and is considered, perhaps a luxury service. It is true that the latter countries are mostly in need of services to combat infectious diseases and such personal services are still beyond their economical and technical capabilities. It cannot, however, be denied that some of these countries are making considerable headway on these lines and are including more and more personal services in their health programme. Fortunately, India has brought down the incidence of infectious diseases in certain areas and has undertaken the task of eradication of malaria, smallpox and cholera in the next few years.

Improvement of health services in West Bengal during the last ten years (1948-58) has resulted in (i) reduction of death rate by 50 per cent, (ii) saving the lives of 2 lacs of its population, and (iii) increase in the span of life by 10·74 years. In the over-all attempt of providing better health services, both preventive and curative, it is expected that the people will enjoy health and live a long and useful life in years to come. The experts on health may differ in their estimate of the time but all agree as to the ultimate success.

CHANGE IN ATTITUDE

In India, by convention and custom, aged persons are the responsibility of the next generation, but the joint family system of India is quickly changing under the stress of modern civilisation and economic inflation. Such changes in the social and family structures are bound to make individuals self-centred. In advanced years of life these individuals, deprived of the physical and economic strength, will suddenly feel perhaps a bit lonely and helpless and will need help of a nature very different from those of early life. He will look forward for guidance and help, not for revival of his youth but for making his life useful and comfortable.

On a modest estimate, 6 per cent of the total population in India, i.e., about 2,10,00000 persons will be above 65 years. Can any health programme be planned without making provision for such a large number of persons who will need some form of health service. This is in contrast with any other age group, where medical care consequent to sickness is meant for only a small fraction of the total population in that age-group, perhaps with the solitary exception of the newborn. If the goal of the modern health services is based on Winslow's definition of "preventing disease, prolonging life, and promoting physical and mental efficiency, through organised community effort" and "the extension to all people of the benefits of the medical knowledge and facility", then it is imperative that geriatrics should form a part of our health programme.

Need for a New Orientation

With major emphasis on infectious diseases and their prevention, facility for the training of the medical and ancillary personnel is limited. With the introduction of 'health centre' movement it has been found difficult to get suitable men to serve as medical officers of such centres. Integration of preventive and curative services appears rather foreign to such persons because such integration was unknown in their student days. It is desirable that the planners of medical education and health services should think a few years ahead of their time and orientate the teaching not only in terms of the present services but also of future ones. Otherwise there is bound to be a gap between production and requirements both in quality and quantity. The emphasis on sanitation and infectious diseases may not have the same value a few decades hence. Quite a few may have to take up work like rehabilitation of cerebral palsy, rehabilitation of fractures of old persons, etc.

Survey

In India, the statistical and epidemiological information regarding gerontology is undoubtedly very scanty. An attempt to collect such information in carefully selected samples (both urban and rural) and a longitudinal study for a number of years may yield fruitful results that will be useful for that area. Concurrently, physiological, pathological and psychological changes in the aged should be investigated so that concrete steps may be taken for prevention and alleviation of the sufferings of old age.

Research

Researches into the problems of ageing in our country have not yet been taken up systematically. The physiology of the old is not the physiology of the young, and the problems of the old and the young are not the same. If we are to study man in relation to his environment, it is essential that we must have sufficient knowledge of the influence of environment on health in different age groups. The social, environmental, economic and familial influences are of a different nature in India and the qualitative and quantitative estimates of those influences are little known. Attempts, first on research and then on service, should be made to find out the real need of the aged. It must be remembered that dyspepsia and flatulence in the old have also a definite epidemiology. Explanations like idiopathic or psychosomatic should no longer stand in the way of scientific enquiry. Such explanations conceal our ignorance and tend to discourage inquiry into the aetiology. The mysterious ageing process is decisively influenced by certain factors like some infections in early life, some physical and social environments. Some of these are curable and some preventable. The control of infectious diseases, which are responsible for organic impairments of the heart and degenerative processes of other organs of the body, is an important aspect in checking so-called 'senescence' which will unfortunately permeate into a large segment of our population. Occupational exposures, nutritional deficiencies and excesses are factors which are now known to influence the 'ageing process' and are not beyond the purview of prevention. Emotional disorders resulting in maladjustment in social and family life are on the increase. Socio-economic status is being increasingly recognised as a major factor in so-called 'ageing' and chronic old age maladies.

A Separate Discipline

The establishment of a separate department of geriatrics, though highly desirable, may not be possible for all teaching institutions, but incorporation of the subject with other departments is not impossible. The department of medicine or the department of preventive and social medicine may be saddled with the responsibility of teaching geriatrics both at undergraduate and postgraduate levels without altering the present set-up to any marked extent. A cursory glance at the question papers, set for the undergraduate and postgraduate examinations, will show that questions on this subject are on the increase. These questions did come as offsets of questions on general medicine and this is a very natural way of recognising a speciality.

Geriatrics, then, has a rightful claim of a speciality. Diseases like rheumatoid arthritis, rheumatism, senility, chronic degenerative process, neoplasms, etc., are some of the problems which have been tagged with geriatrics in other countries —not because they are problems of geriatrics alone but because they are generally also the problems of old age. Services to be rendered by the State have increased enormously with the concept of medical care, as against treatment alone. If services demanded of the profession are to be of a high standard, proper facilities for teaching the subject must be provided. This can be possible by apportioning more emphasis to the subject and its inclusion in teaching.

A tentative programme may be drawn on the following lines:

(*a*) Research,
(*b*) Training of personnel,
(*c*) Service.

The programme should include: (*i*) adequate provision for and intelligent care of the sick, (*ii*) prevention and relief of destitution, (*iii*) protection of dependants, (*iv*) intelligent understanding and treatment of the problems of old age, (*v*) organisation of nursing and clinic services, and (*vi*) recreation and education with emphasis on rehabilitation.

Teaching Responsibility

Medical care and prevention are things which clinical departments under the present set-up cannot provide even for a short period. Only an integrated approach can solve the problem. Psychosocial maladjustment has been assessed to be the core of problems of the aged. Consequently, the care lies in the home and not in the hospital. The Preventive and Social Medicine department, if organised properly envisages care within and outside the hospital. So far as is known, the P.S.M. department of different medical colleges in India has not been attotted any clinical responsibility. Medical education comprises both theoretical and practical teaching. Hence indoor teaching facilities are as important as outdoor and community field practice. The P.S.M. department admirably fits into the role if some clinical responsibility is attached to it. Geriatrics can very well be the starting point of integration of clinical and domestic care programme under the responsibility of P.S.M. department.

Summary

The importance of geriatrics has been discussed. It has been shown that in the near future the higher age-group individuals will need more medical care in respect of both quality and quantity. Training in the undergraduate and postgraduate levels should, therefore, include more and more information on this speciality. As such, a separate department is considered a step in the right direction. It is suggested, that either the department of medicine or the department of P.S.M. be adequately organised and staffed to take up the additional responsibility of teaching and research in geriatrics. The P.S.M. department is admirably suited to be entrusted with the new burden, as geriatrics is not confined to hospital services alone but it includes within its purview factors like psychological, socio-economic rehabilitation, etc.

ACKNOWLEDGMENT

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CASE NOTE

ORONASAL REGURGITATION OF FOOD FOLLOWING SORE THROAT

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A male, aged 36, after an exposure to heat took a glass of refrigerated cold water. Next day he experienced soreness of the throat without constitutional symptoms.

There was coryza and redness of the oropharynx. The patient had a temperature of 101°F. He was given injections of sodium penicillin, 500,000 units, intramuscularly every 12 hours. Hot saline gargle and hot liquids were recommended.

On the following morning the patient complained of regurgitation of food (both solid and liquid) through the oronasal apertures. Slight congestion of the throat and nostrils was found on examination. There was paresis of the muscles of the oropharynx as much as was visible. There was no hoarseness of voice. The temperature was 97°·4F orally. There was no egophony, no ptosis and no other constitutional symptoms. Thinking him to be a case of cold affecting the nerves supplying the muscles of the oropharynx he was given an injection of 1·1 ml. of prostigmin, I.M., to judge its therapeutic response and thereby helping diagnosis. Within five minutes, when the patient was asked to swallow some food, both solid and liquid, he swallowed them with the least difficulty. He was then advised to continue injection of sodium penicillin, 500,000 units, intramuscularly every 12 hours, for the next 48 hours, and prostigmin tablet, 7·5 mg. orally, 12 hourly for 48 hours.

He had no further recurrences. After seven days, and again after fifteen days of the treatment he was checked up for evidence of any paresis which was found completely absent since the prostigmin injection.

ALL-INDIA MEDICAL CONFERENCE

It is learnt from the Central Office and the President of the I.M.A. that earnest attempts are being made to hold the 37th All-India Medical Conference in March 1961. The venue and the provisional dates will be announced in this Journal at the earliest opportunity.

P. K. Guha
Hony. Editor, *J. Indian M.A.*

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INTRAVENOUS INJECTION OF OXYGEN

Many attempts have been made in the past to oxygenate the blood by routes other than the pulmonary. The only method by which any considerable quantity of oxygen can be introduced into the blood by an extrapulmonary route is by intravenous injection. The amount that can be thus introduced under normal conditions is very small—about 25 per cent of the total requirement in dogs and 5 to 6 per cent in human beings. There are however two methods by which it is possible to supply all the oxygen requirements of dogs by the intravenous route. The first method is by increasing the atmospheric pressure under which the experiment is performed[1]. It is well known that in the treatment of caisson disease the patient is put back into the caisson under increased atmospheric pressure, so that the bubbles which are released on decompression are dissolved on recompression. It follows therefore that if bubbles of gas are artificially introduced into the blood, they will dissolve if the atmospheric pressure under which the experimental animal is placed, is increased. Using this technique, it was found[1] possible to keep a dog alive without breathing oxygen through the lungs for 6 minutes by injecting oxygen intravenously under a pressure of 4 atmospheres.

The second method is to lower the oxygen consumption by hypothermia to such an extent that it equals the amount of oxygen that can be injected intravenously[2]. This can be done if the body temperature is lowered to 20°-22°C ; the oxygen consumption falls to 1-2 c.c. per kg. per minute, which is equal to the intravenous dose of oxygen. It was possible to keep 4 dogs alive for 20 minutes without breathing oxygen through the lungs.

Oxygen was first injected intravenously in 1811[3]. Using dogs 20 c.c. of oxygen was injected per minute, and repeated every 3 to 4 minutes. A dose of 30 to 40 c.c. per minute was found to be fatal. In the same year intravenous oxygen was given to dogs by another worker[4]. In 1902 oxygen was given intravenously in doses of 1-2 c.c. per kg. of body weight per minute, into a living human being[5]. 80 c.c. of oxygen was injected intravenously in half an hour into a dying phthisical patient. Oxygen was also given to a dog of 15 kg. body weight at a rate of 3 c.c. per kg. per minute for two hours[6]. In 1916, 10 to 20 c.c. of oxygen per minute was administered to three patients[7] for 10 to 15 minutes, separated by pauses of 2 to 3 minutes. The dose for dogs was found to be 1 to 3 c.c. per kg. of body weight per minute[8, 9]. In 1940, 10 to 20 c.c. of oxygen was administered intravenously to six human patients with success[10]. Intravenous oxygen was given to human patients at the rate of 200 to 600 c.c. per hour with beneficial results[11]. Intravenous oxygen was given to 12 dogs at the rate ranging from 0·21 to 3·17 c.c. per kg. per minute without any benefit, and the fatal dose in one dog was found to be 3·2 c.c. per kg. per minute[12]. Oxygen adminis-

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[9] Dick, M.—*Ibid*, **127** : 228, 1939.
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tered intravenously to dogs for 10 to 14 hours at the rate of 100 c.c. per hour showed great improvement in haemorrhagic shock[12]. It was also given to three human patients at the rate of 60 to 6000 c.c. per hour, in quantities ranging from 7,000 to 18,000 c.c.[13]. Oxygen was also given to six patients without any beneficial result[14]. With another worker[15] intravenous oxygen given to patients showed limited success and small quantities of this gas gave remarkable anti-shock properties. It could be administered with relative safety.

Metabolism is reduced in hypothermia if shivering is avoided[16, 17, 18]. During hypothermia, therefore, it would be possible to provide a greater fraction of oxygen requirement by the intravenous route. In hypothermia, there are two opposing factors that affect the intravenous injection of oxygen. During hypothermia, the solubility of oxygen in the plasma is increased by about 50 per cent[19]. Sluggishness of the circulation gives greater time for the absorption of oxygen. These two factors favour intravenous injection of oxygen. Sluggishness of circulation acts in opposite direction also as the oxygen accumulates in the veins and does not move forward fast enough. Therefore it is expected, that at a certain temperature the intravenous injection of oxygen should b maximum. This has been realised experimentally[20]. It was found in dogs that at 25°C body temperature, the maximum amount of oxygen could be injected intravenously. The last work advocates replacement of pulmonary oxygenation of blood by the intravenous route completely.

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GERIATRICS

Health is no longer an individual or a family concern as it was fifty years ago. A new doctrine has evolved enunciating the role of the state in preservation and promotion of health. It is a matter of right that the health of everyone is brought up to a higher level. Sir Arthur Newsolme concluded that (1) the health of every individual is a social concern and responsibility, and (2) medical care in its widest sense for every individual is an essential condition of maximum efficiency and happiness in a civilised community. Based on this new doctrine, complete medical care for everyone in a community is a goal which every nation is striving hard to attain. It is very timely to draw the attention of medical and health workers to a problem which seems neglected in India. The care of the old and the aged is a type of personal service which has not so far drawn much attention from the leaders of health. That there is ample justification for immediate inclusion of geriatrics as a speciality in India, is brought out in an article in this issue[1]. In view of the large number of persons who need special care, as also, the complexity of the related medical aspect, it seems justifiable to suggest that the medical profession in India should rise to the occasion. Great Britain, U.S.A. and some other advanced western countries have already achieved phenomenal success in making their elderly people suffer less and enjoy more of life. Research, organisation, and co-operation have made it possible. India cannot afford to lag behind. It is already time that the subject is taken up in all seriousness and every effort made to provide adequate medical care for an apparently neglected age-group.

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I.M.A. PRESIDENT'S VISIT TO BRANCHES

On October 6, 1960 the Bombay Territorial Branch arranged a reception at the Airport in Bombay for the members returning from Europe after completing the third study tour to Russia and Europe. In the evening the Bombay Territorial Branch arranged a dinner at the Willingdon Sports Club, Bombay, at which Dr. H. N. Shivapuri, President, I.M.A. and Dr. Mehra were the chief guests. Dr. Shivapuri spoke at the meeting of his experiences in the various countries of Europe. He also appealed for further contributions by I.M.A. members at Bombay towards the Indian Medical Association Building Fund and they promised to do their best.

On October 14th and 15th Dr. Shivapuri visited Indore in connection with his work as a member of the Sub-Committee appointed by the Medical Benefit Council of the E.S.I. Corporation.

On the 14th instant the Indore Branch of the Indian Medical Association arranged a general meeting of the Branch at the Medical College, Indore. Dr. G. S. Wagle, President of the Madhya Pradesh State Branch and of the Indore Branch of Indian Medical Association, presided. Dr. Shivapuri addressed the members and appealed for the payment of their quota for the Indian Medical Association Central Building Fund.

On the 16th October Dr. Shivapuri accompanied by Dr. G. S. Wagle and Dr. R. A. Bhagwat visited Dhar Branch of the Indian Medical Association from Indore. A nice lunch had been arranged by the Dhar Branch in the Circuit House, Dhar, and an At Home was given in the afternoon. Dr. Shivapuri addressed a very well-attended meeting of the members of Dhar Branch at the Dhar Hospital in the interval between the Lunch and the At Home. The members of Dhar Branch discussed several important matters with him including the Central Building Fund and they promised their help in collecting funds from Dhar for the Central Building Fund of the Indian Medical Association. It was Dr. P. Sharma, the Secretary of Dhar Branch, who invited the President to Dhar and in spite of his ill health arranged this meeting.

On October 22nd and 23rd the President visited Varanasi in connection with the 25th U.P. State Medical Conference and inaugurated the Conference. Here also he appealed to the members to collect money for the Building Fund of the Indian Medical Association and felt sure that more money would be flowing from U.P. towards the Funds.

On 28th, 29th and 30th October the Eighth meeting of the Central Council of Health (Health Ministers' Conference) held at Jaipur was attended by Dr. Shivapuri. On October 29th the Jaipur Branch of the Indian Medical Association arranged a meeting of the Branch in order to enable the members to meet the President. At the meeting Dr. Shivapuri spoke on some of his experiences of Europe as also some of the important matters affecting the medical profession. He also appealed to the members to donate as much fund as possible to the Central Building Fund of the Indian Medical Association. The members of Jaipur Branch promised to do their best and he hoped to have good response from them. After the meeting, an At Home was given jointly by Rajasthan State Branch and Jaipur Local Branch in honour of the meeting of the Central Council of Health. All those who came to attend the meeting of the Central Council of Health including Shri Karmarkar, Union Minister of Health, and other State Health Ministers and their Staff attended the At Home.

On 31st October 1960 the President proceeded to Alwar (Rajasthan). The Branch at Alwar was originally formed by Dr. Shivapuri when he was State Secretary of the U.P. State Branch and for years it continued to be part of U.P. State Branch till it was handed over to Rajasthan State Branch when that State Branch was formed. Alwar Branch arranged a dinner meeting which Dr. Shivapuri addressed. *The Alwar Branch had practically completed their quota of Rs. 50/- per member for the Central Building Fund of the Indian Medical Association.* This is an achievement to the credit of this Branch which is one of the few in the country which has done so. In spite of this as a result of the appeal from the President they promised to do more.

On November 1, 1960 Dr. Shivapuri went to Agra at the invitation of the Secretary of that Branch. A meeting of the members held in the evening was addressed by him. He spoke on some of his recent experiences in Europe, as also on some important matters affecting the profession. He appealed for contributions to the building fund of the Indian Medical Association and hoped to get a good amount of money from Agra Branch for the Building Fund including about one thousand rupees as donation. The Secretary of the Branch, Dr. S. K. Das, and the President, Dr. K. S. Mathur, deserve praise for their promise to sponsor the cause.

On November 18, 19 and 20, Dr. H. N. Shivapuri had been to Ranchi in connection with the 20th Bihar State Medical Conference. He unfurled the I.M.A. flag and installed the new President of the Bihar State Branch. He also inaugurated the Scientific Section of the Conference.

GENERAL PRACTICE DIGEST

THE PRESENT STATUS OF PARA-AMINOSALICYLIC ACID (PAS) AND ITS DERIVATIVES

Para-aminosalicylic acid (PAS) is extensively used in the treatment of tuberculosis. It is bacteriostatic, but the mechanism of its action is different from that of isoniazid. When given in combination with streptomycin, it is necessary to administer 20 g. of PAS daily to produce the maximal suppression of streptomycin-resistant tubercle bacilli. For patients who are troubled with side-effects, it is advisable to reduce the daily dose to 15 g. PAS can also be prescribed with isoniazid. As PAS is rapidly excreted, it should be given four times a day in equal doses. It is best given with or immediately after a meal. When the patient is recovering and is ambulant, the drug can be given twice daily (i.e. after breakfast and after supper) in combination with isoniazid. To prevent a relapse, the treatment with even minimal pulmonary tuberculosis must continue for at least 12 months whatever drug combinations are used, and in extensive cases 2 or more years of continuous treatment are required.

When using isoniazid plus PAS therapy in children the daily dose of PAS is calculated on the basis of 1 g./pound (160 mg./Kg) body weight. It is given as a freshly prepared solution "disguised" with syrup of orange and 1 g. of PAS is contained in 8 ml. of the mixture. This mixture is followed by a pleasantly flavoured isoniazid syrup. Gastro-intestinal disturbances, rashes and other side-effects are rare. Generally, the younger the child the less is the intolerance.

Side-effects—The incidence of side-effects is related to the size of the dose. The common gastro-intestinal disturbances are nausea, abdominal discomfort and mild diarrhoea. They tend to improve if the treatment is continued. Some patients manage better with one day of rest each week without PAS. The drug rashes (with or without fever) may be urticarial, morbilliform or erythematous, and rarely exfoliative. They are often controlled by antihistamine drugs; but if they fail then either PAS must be replaced by another anti-tuberculous drug or else desensitization must be attempted.

After 6 months or more of PAS treatment there is often a generalised mild thyroid enlargement, especially in young women. Occasionally myxoedema develops. More usually the goitres are symptomless and subside with cessation of treatment. PAS myxoedema rapidly improves on medication with thyroid extract.

Among the rare side-effects may be mentioned agranulocytosis, eosinophilia, and a blood picture resembling that of glandular fever. Thrombocytopenic purpura and eosinophilic transient lung lesions (like Loeffler's syndrome) have been met with. Jaundice from toxic hepatitis is unusual, but symptomless hypoprothrombinaemia have been seen. Hypokalaemia with cardiac irregularities and transient paralysis has been reported.

PAS derivatives—'Paramisan sodium' (sodium aminosalicylate) is available in the form of cachets, each containing 1·5 g. of PAS. 3 cachets may be given four times a day (18 g. daily) with streptomycin injections. For those who cannot swallow cachets or in whom PAS causes nausea and vomiting, 0·5 g. sugar- or enteric-coated PAS tablets or 'Pasade' granules are recommended. 'Pasade' granules contain PAS intimately mixed with a special type of fat. After swallowing the fat melts and forms a coating to the stomach which protects it from irritation by the liberated PAS. Each 500-g tin contains a scoop holding 2·5 g. of PAS.

In order to prevent isoniazid-resistant organisms, PAS and isoniazid should be combined. 'Pycamisan' cachets contain both PAS and isoniazid. Eight cachets of 'pycamisan PH 10' daily give a daily intake of 10 g. of PAS and 200 mg. of isoniazid.

'Dipasic' is a chemical combination of isoniazid with PAS. It is ineffective and should not be used.

'Calcium benzoamidosalicylate' is a chemical union between calcium PAS and benzoic acid. It is marketed as 'therapas' as 1 g. or 3·5 g. cachets. It is given with isoniazid in dosage of 10·5 to 14 g. daily. When given with streptomycin 21 g. a day is advisable. The 'therapas' packet is emptied into a glass of water or milk, stirred up to form a suspension, and swallowed as a draught. Another preparation is 'therazid' each packet of which contains 3 g. 'therapas' and 75 g. isoniazid, and each cachet contains 1 g. 'therapas' and 25 g. isoniazid. Four packets or 12 cachets of 'therazid' should be used daily.

Test for PAS in urine—Add a few drops of normal hydrochloric acid to 1 ml. of urine, followed by a 10 per cent solution of ferric chloride drop by drop. If PAS is present a purple colour results, varying from almost black to a light purple shade, according to the concentration of PAS in the urine.

A 'dip and read' paper reagent strip known as 'phenistix' is also available. Urine containing PAS turns it to distinct purple colour.

Both these tests give a similar purple colour with salicylates and with metabolites of chlorpromazine.

Remarks—PAS is mildly tuberculostatic, but it helps in preventing the emergence of resistant strains of *M. tuberculosis* when it is given in conjunction with one or more of the other anti-tuberculous drugs. It should not be given as the sole drug. Children tolerate PAS better than adults.

—From an article by M. O. J. Gibson, *Practitioner*, **185**: 228, 1960.

CURRENT MEDICAL LITERATURE

Acute Adrenal Insufficiency After Steroid Therapy

STEVENS, A. R. (*Lancet*, **2**: 234, 1960) from Canadian Red Cross Memorial Hospital, Taplow, Bucks, writes that acute adrenal insufficiency associated with pneumonia developed in three asthmatics who had had steroid therapy. Symptoms and signs of infection were overshadowed by those of hypoadrenal collapse. Two patients recovered after supportive therapy. The importance of early recognition and treatment of such cases is stressed.

Acute Haematogenous Osteomyelitis

WINTERS, J. L. AND CAHAN, I. (*J. Bone & Jt. Surg.*, **42A**: 691, 1960) from the Department of Orthopaedic Surgery, Louisiana State University School of Medicine, New Orleans, from the analysis of the study of 66 patients with acute hematogenous osteomyelitis admitted to Charity Hospital during the period January 1, 1956, to May 1, 1959 observe:

A review of all the patients with acute hematogenous osteomyelitis was undertaken to verify the clinical impression that this disease is increasing in frequency and changing in character. Sixty-six patients were seen during this time and are included in this study. A significant increase in the incidence of acute hematogenous osteomyelitis has occurred in southern Louisiana over the past four years. This increase in incidence has been ascribed to the increasing number of bacteria resistant to the usual antibiotics and particularly to the resistance of *Staphylococcus aureus* to penicillin.

In contrast to previous reports the sex distribution in the series was almost equal. Twenty-three per cent of the patients were one year of age or less.

Staphylococcus aureus was identified in 90 per cent of the patients in whom positive cultures were obtained. *Streptococcus haemolyticus*, contrary to many early reports, was not identified as the aetiological organism in any of the infants.

One-third of the patients under review was admitted with a very mild form of this disease and had no significant fever or other systemic manifestations.

Treatment consisted in antibiotics, immobilisation, and surgery when indicated. Despite what was considered adequate treatment in almost every instance, chronic osteomyelitis developed in 29 per cent of the patients in this study who were adequately followed. The authors maintain that early but inadequate antibiotic treatment caused an increased tendency to the development of chronic osteomyelitis.

Additional emphasis should be placed upon the basic orthopaedic principle of immobilisation. In this survey complications developed in the majority of the patients who were not treated initially by immobilisation.

Antibiotics have unquestionably decreased both the mortality and morbidity associated with acute hematogenous osteomyelitis. Nevertheless, as more bacteria become resistant to our common antibiotics, the incidence of chronic osteomyelitis will continue to increase. Perhaps more liberal utilisation of early incision and drainage in those cases which are prone to become chronic, as evidenced by slow indolent progression of the local lesion, may improve the present results.

Congenital Myopia

Myopia can be divided into three types—simple, progressive or degenerative, and congenital. The first two groups develop during childhood, usually after the age of 4 years (though sometimes degenerative myopia has an earlier onset), whereas the congenital type is present at or soon after birth.

Simple myopia usually varies from 0 to 6 dioptres. It is classified in the biological series of refractive errors and involves no pathological changes.

Degenerative myopia is now thought to be genetically determined. Commonly it progresses to chorioretinal degeneration and sometimes to retinal detachment. In the worst cases blindness ensues in middle age.

Congenital myopia includes several groups of disorders, some non-progressive and others leading to degenerative changes.

Congenital mypopia is sometimes accompanied by obvious congenital defects, such as posterior staphyloma, coloboma, albinism, or generalised growth anomalies associated with defects of the pituitary gland or the gonads. In other cases the myopia is found in children who have been prematurely born, as a manifestation of mild retrolental fibroplasia; the myopia varies from 2·5 to 20 dioptres and is usually non-progressive during childhood. Cases have also been described in small premature infants where there is no retrolental fibroplasia and no family history of myopia. Drillien has stressed the high incidence of congenital myopia in infants of very low birth-weight. Of 43 children who had weighed 3 lb. or less at birth, 11 were myopes and most were of poor mental ability.

Often myopia is present in small premature infants in the early weeks after birth, and the vision reverts to normal by 3 to 6 months. Whether congenital myopia is sometimes due to persistence of immaturity of the eye into childhood is unknown. Further work is needed on the nature of the myopia, to determine whether it is due to changes in the cornea, lens, or vitreous, or to an abnormal axial length.

Gardiner and James have lately suggested that maternal disease in pregnancy may be a factor in causing congenital myopia. In a series of 38 cases of myopia of more than 4 dioptres in school children, they found that 50 per cent of the mothers had had toxaemia, hypertension, or renal disease in the pregnancy ending in the birth of these children, while in a control series of children who had visual defects other than myopia, only 13 per cent of the mothers had had toxaemia or hypertension. There was no association with prematurity in the myopic series, but it is not clear that the myopia was congenital. As Gardiner and James point out, there are indications that foetal environment is not normal in toxaemia; both blood-flow through the placenta and oxygen saturation in the umbilical vein are reduced. Adequate nutrition in childhood is recognised as a factor in slowing deterioration in progressive myopia; and, conversely, inadequate nutrition in utero might promote congenital myopia. A long-term follow-up of cases of congenital myopia in full-term and premature infants is required before any conclusions can be reached. Cases must be diagnosed in the first 2 years of life, and those with a family history of myopia must be excluded. Such a prospective survey would enable physical and mental defects to be correlated with the clinical history of pregnancy, delivery, and postnatal development. (Annotation, *Lancet*, **2**: 14, 1960).

CURRENT TOPIC

AIR POLLUTION

In December 1952 many parts of the British Isles were covered by an anticyclone. It was cold, and fog was widespread, particularly in and around London, which remained blanketed in it for five days. Within about 12 hours from the beginning of the fog the morbidity rate in the Greater London area became very much higher than usual for the time of the year. The common form of illness experienced was characterised by a relatively unproductive cough, nasal discharge, sore throat, and sudden attacks of vomiting, and was especially severe in persons who had had a previous history of chest trouble. In the very ill, dyspnoea, cyanosis, moderate fever, and râles and rhonchi indicative of bronchospasm and the presence of bronchial secretions were present. Men were affected more than women, and most of the sick were over 45 years of age. There were appreciably more hospital admissions than usual, particularly for cases of acute respiratory infection but also for heart disease. The mortality records showed that, during the week of the fog and the week after, there were 4000 deaths more than the average. Most of the people who died were recorded as having had chronic bronchitis, bronchopneumonia, other lung disease, or disease of the heart.

During the fog the smoke concentration was found to be five times greater than at other times; the sulphur dioxide concentration about six times greater. A Committee on Air Pollution set up in 1953 by the Government of Great Britain "to examine the nature, causes and effects of air pollution and the efficacy of present preventive measures" held that, while the evidence did not provide a clear indictment of any one constituent of the fog, the conclusion was inescapable that the excessive mortality and increased incidence of respiratory infection during and immediately after the fog were the result of irritation of the respiratory tract by contaminants of the fog—the irritants mainly responsible probably being derived from the combusion of coal and its products and their lethal effects being almost wholly exercised on persons suffering from chronic respiratory or cardiovascular disorders.

This was not the first time that air pollution has been blamed for producing ill effects on health in London. The English Parliament had passed an act as long ago as 1273 forbidding the burning of coal in London, and in 1306 a man was executed for doing so. The law quickly fell into abeyance as the shortage of wood as fuel became more pronounced, and when the Industrial Revolution came attempts to prevent the pollution of the atmosphere were unavailing. Towards the end of the nineteenth century big increases in mortality occurred in association with periods of severe fog in 1873, 1880, 1882, 1891 and 1892.

Air pollution and its evil effects were not, and are not, confined to England, the home of the Industrial Revolution. There was a notorious occurrence in 1930 in the Meuse valley in Belgium, associated with anti-cyclonic conditions, cold, fog, and heavy industry. In 1948 the industrial town of Donora, USA, some 30 miles south of Pittsburg, was afflicted by a heavy fog from 27 to 31 October; 8910 persons (42·7% of the population) fell ill, 13·5% mildly, 16·8% moderately, and 10·4% severely; 17 persons died. There was also the Poza Rica incident of 1950 in Mexico. Mention should be made, too, of the recurrent "smog" of Los Angeles, occurring during the summer and early autumn and causing irritation of the eyes, nose and throat, damaging vegetation, and making the atmosphere hazy.

Wherever men collect they tend to pollute their environment. Throughout human history towns have been concentrations of refuse and dust, with rivers and wells polluted by waste materials, and ground water contaminated—and, as a corollary, they have been breeding-grounds for vermin and bacteria and centres of epidemics. The dangers of impure water and the indiscriminate disposal of sewage and refuse have slowly been recognised, however, and it is safe to say that practically all towns of reasonable size in the world pay at least lip service to the ideals of pure water and sanitary disposal of sewage and refuse.

Only relatively recently has so much attention been paid to pollution of the air. The biological processes of living matter, certain natural phenomena and many of man's activities—especially since the Industrial Revolution—result in the liberation of gases, vapours, dust, and aerosols of suspended particles into the air, and some of these almospheric contaminants are harmful to health. The study of the nature, properties, and behaviour of the contaminants is difficult, and requires the co-operation of physicists, chemists, and biologists; the polluting gases and vapours may form a proportion of only a few parts per million or even one part per thousand million or less, but the toxicity of some compounds in the parts per thousand million range may be greater than that of others in the parts per thousand range. Some of the contaminants have not been identified, and it will be years before full information becomes available on many aspects of air pollution, so complex is the subject, so many and changing the factors involved. Whereas the industrial hygienist works in a semi-closed atmosphere where concentrations are higher than in the street, and conditions are somewhat simpler, so that sampling processes lasting only a few minutes are usually sufficient to give him a picture of what is taking place in the factory, sampling processes in the open air must usually continue for months and often for years before the factors involved in air pollution are understood. Thus the forms of pollution encountered in Los Angeles since 1945 are still not well understood, although measurements have been proceeding for over ten years.

Nevertheless, an appreciable amount of knowledge exists about air pollution and its effects on human health. This knowledge is summed up in a WHO monograph that has just been published. In this volume, which is the work of an international group of experts, a historical review of atmospheric pollution is followed by sections on sampling and analysis of the contaminants, the instruments used, the physical and chemical nature of air pollution, the role of meteorology, the effects of air pollution on human health, animals, and plants, the economic and social aspects of air pollution, the control

of pollution by site selection and zoning and by process changes or equipment, fuel selection and utilisation, air pollution legislation, standards, and enforcement, and finally—and topically—radioactive pollution of the atmosphere.

By the end of the nineteenth century practically everything that is now known about the causes of smoke—the visible cloud of suspended carbon particles that is the first and most obvious of the pollutants of the air—and its elimination had already been said in Great Britain. But smoke was not eliminated because it is a by-product of activities producing goods and profits and thus commanding the attention and support of financial interests. Moreover, the damage done by smoke, though considerable, was not very clearly visible to the individual smoke producer because widely spread, and since the damage was due to a large number of small producers a clear relationship between cause and effect was not easy to establish; nor, for the same reasons, could the blame readily be pinned upon definite persons who could be asked to remedy the situation. In American cities a few decades later it was found that even when public opinion was convinced of the need for smoke reduction there was reluctance to take the necessary measures, the attitude always being that the responsibility for doing so was someone else's. Circumstances have helped some countries in the campaign to abate the smoke nuisance: in the USA supplies of oil and natural gas, which burn with little or no smoke, became more freely available. Even so it became necessary for states and municipalities to pass laws to make it compulsory for householders and industries to burn smokeless fuels or to use more efficient equipment to burn fuel. In Great Britain there was no natural gas; oil had to be paid for in foreign currency; and even if industries could be compelled to install more efficient machinery for getting rid of smoke the main problem would be to prevent the domestic consumer of coal from continuing to burn it wastefully in open grates. A considerable proportion of the air pollution of the great fog of 1952 in London was attributable to smoke from fires burning in innumerable open grates throughout the metropolis.

Smoke is not by any means the only atmospheric pollutant. Grit and dust, sulphur dioxide from coal and smelters, hydrochloric acid from such processes as the production of sodium carbonate from common salt, hydrogen sulphide from tar distillation, nitrogen dioxide from the chamber process for sulphuric acid, hydrogen fluoride from the production of superphosphate and aluminium, lead, arsenic, zinc and copper derivatives from the metallurgical industries, finely divided beryllium from the manufacture of radio valves, hydrocarbons, aldehydes, and olefines from combustion of oil, carbon monoxide from a variety of sources, all enter the air to join the sulphur dioxide, hydrogen fluoride and hydrogen derived from volcanic disturbances, the hydrogen sulphide from seepage of natural gas, volcanoes or action of sulphide bacteria, the ozone formed photochemically or by electric discharge, the dust and aerosols consisting of salt particles from sea water, particles from soil and vegetation dust of meteoric origin, bacteria spores and pollen. The concentration of the substances not contributed by man is extremely low, except in the immediate vicinity of natural sources, but the concentration of those contributed by man can, meteorological conditions aiding or in the industrial centres themselves, be high enough to be injurious to health, and has been the subject of much industrial legislation. This legislation has on the whole been concerned with conditions in the factory or workshop itself, not to any great extent with conditions outside.

The complete list of atmospheric contaminants that are harmful to the health is not known. In Los Angeles it was at first thought that sulphur dioxide was the main irritant in the smog, but now the list of substances currently considered to be causally related includes as well oxides of nitrogen, aldehydes, ketones, acids, chlorinated hydrocarbons, acroleins (or an "acrolein-like substance"), chlorinated aldehydes and related substances, formyl compounds, ozonides and peroxides of hydrocarbons of the series present in gasoline (especially the straight-chain hydrocarbons containing double bonds), ozone, nitro-olefines, peracylnitrites, organic free radicals, and carbon suboxide. This is a formidable list, but it is not exhaustive. It is considered that the gases and aerosols discharged into the air may not be irritant in themselves but may be acted upon by the ultraviolet rays of the sunlight and the resulting syntheses may be the smog-forming substance or substances. The present view is that the oxides of nitrogen and hydrocarbons (mostly olefines), both arising from combustion processes, especially of petroleum products, are involved in the photochemical changes that take place, with appreciable increase of the amount of ozone, in the air. In other words, more important than the combustion of coal and allied products—which were the main cause of the London fog of 1952—is the combustion of gasoline by the well over 2 million motor cars in Los Angeles, with their consumption of over 8 million gallons of gasoline daily.

A great deal remains to be found out about the effect of atmospheric contaminants on the human body. The biochemical reactions they produce vary: they may corrode, like sulphuric acid; or react with cellular proteins, like the aldehydes. They may be strong oxidizing agents, like ozone, or interfere with enzyme systems within the cell. They may, like the nitro-olefines, affect the eyes and the lungs. They may act on the upper part of the respiratory tract, or aerosols may aid the irritants to gain access to the lower part. Irritation of the upper part may cause reflex spasm of the distant bronchioles and severe symptoms, and very fine particles, generally classified as "inert", may cause bronchoconstriction, apparently by virtue of an unexplained local irritant action. The lining of the bronchi may suffer from interference with its cleansing system, and the secretory rhythm of the mucous glands may be impaired; or there may be severe inflammatory response in the mucosa, with desquamation of the surface epithelium. Hypersensitivity and hyperirritability may occur. The reports on acute air pollution episodes indicate that the damage was due to local action of the pollutants on the exposed membranes, and that, when the respiratory tract was affected in some susceptible persons, secondary

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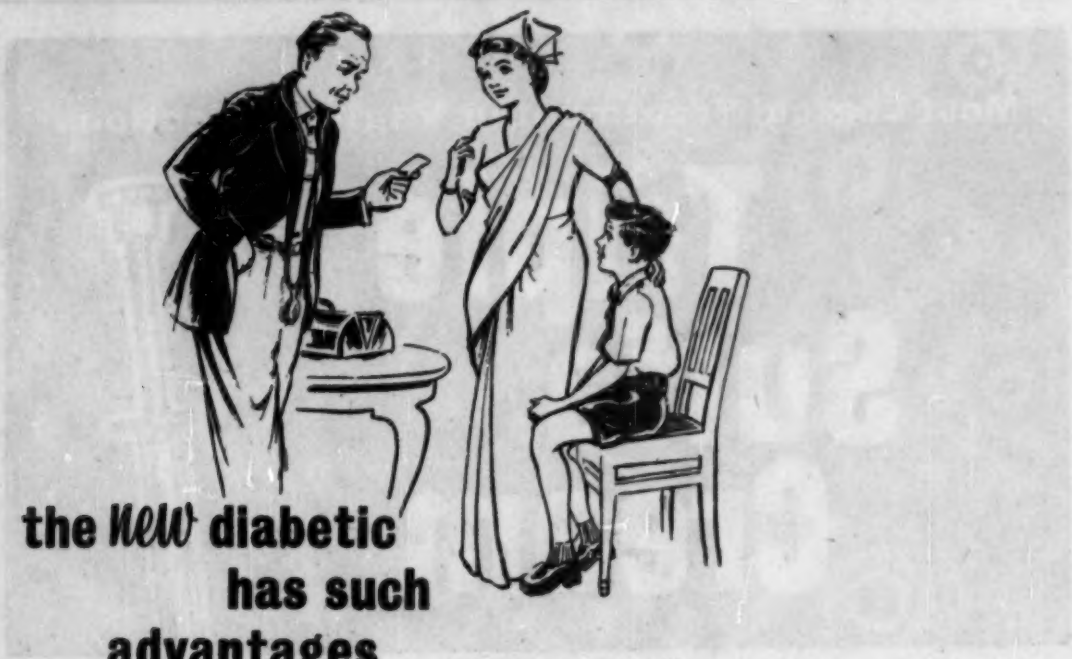

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adverse effects on the heart became manifest. The short-term effects of an increased concentration of atmospheric contaminants on persons suffering from previous disease of the lungs or heart have been shown in the London and Donora episodes; what the long-term effects of these contaminants in lower concentrations may be both on those with previous disease and those without still remains to be elucidated. Among the possible effects is the stimulation of cancer.

Nor does air pollution affect only human health. The economic and social effects are considerable. Livestock and plants suffer; materials and their protective coverings corrode; houses and other buildings need increased maintenance, inside and outside; chimneys, and motors and other engines carry an unburnt residue; technical measures are required to suppress or reduce the smoke or emissions from factories; the removal of dust and the treatment of smoke mean increased use of electric power; transport costs go up in times of smog or fog; more electricity is used for lighting; pollution control requires the organisation of a service to carry it out; research into the many complex problems of pollution cannot be done without funds. The social consequences are not easy to assess. In the United Kingdom, however, they may be seen in the drift of the population from the grimy, smoke-blackened towns of the North of England to the relatively less polluted South, with the vast effects on the community that this may have.

It must not be assumed that air pollution is confined to the industrial nations of Europe and North America, for industry is spreading throughout the world, carrying pollution in its wake. In Mexico City, for example, the average visibility up to 1940 over the city was between 10 and 20 km; now it is hardly more than 4. During fine weather about 5 tons of dust and grit are deposited per square kilometre per week over the city (15 in the centre). Many tropical cities enjoy a climate of warm sunshine and gentle breezes; but this is a positive disadvantage as far as air pollution is concerned, because they are not, like so many industrial towns of more temperate zones, washed and ventilated by rain and wind.

Attempts to remedy air pollution date back in some countries to many years ago, but, as one contributor to the WHO monograph says:

"With few exceptions air pollution control legislation in the various countries is inadequate. A frequent disadvantage is that the first control measures were introduced many years ago, and the legislation at present in force takes no account of the enormous growth of industry, new types of air contaminant, and new sources of pollution, such as motor vehicles and heating installations. Some laws provide solely for the payment of compensation for damage caused by air pollution."

In the United Kingdom a Public Health Act of 1936 constituted as statutory nuisances any industrial installation for the combustion of fuel that did not, as far as practicable, prevent the emission of smoke, and any chimney (except a chimney of a private house) emitting smoke in such a quantity as to be a nuisance. A local authority could serve notice on the offender requiring him to abate the nuisance, and if the notice were not complied with he could be brought before a court, fined, and ordered to comply. Local authorities could also make by-laws regulating the emission of smoke. Unfortunately, the local authorities often did not take action against offenders and failed to use their powers to make by-laws. As a result of the London smog of 1952, however, a Committee on Air Pollution was set up, and a Clean Air Act was passed in 1956 that incorporated many of its recommendations. Under this act it is an offence to emit dark smoke from a chimney for longer periods that may be specified by the Minister of Housing and Local Government; no furnaces other than small ones for mainly domestic purposes may be installed, unless they can be operated, as far as practicable, continuously without emitting smoke; apparatus may be required to be provided to record the density or darkness of the smoke; and smoke control areas may be created. Other provisions cover the height of chimneys, mine refuse, road traffic, smoke from railway engines and ships, grit and dust, pollutants from chemical and other processes, and electricity generating stations.

In the USA there is no general legislation on air pollution, only state or local regulations; but almost every city now has some form of regulation, and it is often more stringent than the law in the United Kingdom, restricting the type and quality of the coals used in hand-fired furnaces and domestic heating appliances, the density of the smoke emitted, or the amount of grit and dust allowable. The result has been an astonishing improvement of the air in some cities, as for example in Pittsburgh.

In most other countries legislation is out-of-date and inadequate to deal with the situation:

"In the present state of knowledge, complete elimination of pollution is not practicable, but there could be much greater improvement than has so far been achieved. Such improvement will only be obtained by better legislation more effectively administered, increasing knowledge based on intensified research and development work, and a more determined public opinion. As new industrial processes are developed and conditions changed, modifications in legislation and methods of enforcement will be required from time to time; but it must be recognised that no one set of preventive measures will meet all needs everywhere owing to differences in the conditions in various countries and localities".

The study of the problem of air pollution has received a new impetus from the arrival of nuclear energy on the world scene, and the great expansion in the use of radioactive materials. The dangers of radioactivity and radium have been used; but these dangers have occurred over the relatively long period in which x-rays and radium have been used; but these dangers have been confined to the laboratory and as much as possible mitigated. The release of radioactive waste into the atmosphere, with its possible effects both on the living and the unborn, has stimulated inquiry into the radioactivity of the air, factors involved in its differing concentrations, the fate of radioactive contaminants, radiobiology and radiotoxicology, methods of measuring

maximum permissible levels, and ways of prevention. This inquiry must result in advances in knowledge of the other contaminants of the air, and it may be that concern about the consequences of radio-active pollution will lead to greater concern about the other forms of pollution as well.

The public health worker should be aware of the problem that air pollution represents. To give some figures for one of the countries where pollution is most serious: in the United Kingdom over a million tons of smoke are emitted yearly from domestic fires; half a million from industry; and 100 000 from the railways. Out of 900 000 tons of grit and dust liberated into the air domestic chimneys emit 100 000. Sulphur dioxide emitted amounts to 5·5 million tons (the domestic fires emitting nearly a million of this). These figures give some idea of the extent of the problem in some countries and the uphill task involved in restoring some measure of purity to the air. It is a task that will need intensive research, the collection and dissemination of knowledge already acquired and to be acquired in the future, the creation of a special administration, the passing of appropriate legislation, and the training of officials in the methods of control. Above all, it will need the backing of public opinion. This can only be obtained by systematic education of the public, by inculcating the feeling that any emission of pollutants into the atmosphere is an offence that cannot be countenanced, whether the offender is industry or the private individual.

—*WHO Chronicle*, **14**: 426, 1960

NOTES AND NEWS

UN Campaign for Birth Control Urged

Well-known scientists from many countries and several Nobel Prize winners on 18-11-60 in a petition asked that the United Nations launch a world-wide campaign for birth control.

The petition signed by 172 outstanding world figures including 30 Nobel Prize winners, was handed to U. N. Secretary General, Mr. Dag Hammarskjoeld by British biologist Sir Julian Huxley and Mr. Cass Canfield, Chairman of the American Organisation for Birth Control.

It said two-thirds of the world's present population was undernourished and stressed that this population continued to increase by some 1,40,000 a day.

In a generation, the petition said, the world's population would double, if there was no change in the current trend.

If a balance between the population and the earth's resources was not immediately established, the world might enter an age of poverty, famine, ignorance and trouble, which could cause panic resulting in wars for the conquest of the remaining riches of our planet, the petition said.

Among the signatories of the petition were France's Andre Maurois, Andre Lwoff and Roger Heim, and P. Avon, Switzerland's R. Mathew and Britain's Sir Charles Darwin.

Nobel prize winners who supported it, included Bertrand Russel and Lord Boyd Orr of Britain, Switzerland's H. Hesse and the American nuclear scientist Harold Urey.

WHO for Co-ordinated Anti-Pox Drive

The inter-regional smallpox conference of WHO which concluded at Delhi on 19-11-60 recommended to the health administration of the countries in the endemic region to "synchronise as far as possible their eradication campaigns and intensify quarantine measures where needed."

The conference, which was attended by the representatives from three WHO regions—Eastern Mediterranean, Western Pacific and South-East Asia, said that eradication of smallpox from the world could only be achieved by "global action to render the disease non-existent and its control redundant."

Smallpox is prevalent in a widespread form in the continents of Asia, Africa and Latin America. As a result of mass campaigns Latin America would be rid of the disease in two to three years. The Indo-Pakistan sub-continent has the highest incidence of the disease, 88 per cent of the cases reported in 1958-59 occurred in this region. Density of population is the prime cause for this high incidence.

The conference expressed the view that smallpox could be eradicated only through mass primary vaccination and re-vaccinations at regular intervals of children up to the age of 15.

The conference suggested that adequate facilities for the supply, distribution and cold storage of glycerinated lymph vaccine was an essential requirement for the success of a mass vaccination programme. Freeze-dried vaccine should be used in place of glycerinated lymph vaccine in countries or parts of a country where there might be difficulties in maintaining the potency of liquid vaccine during its distribution and actual use. In time, dried vaccine might wholly supplant liquid vaccine because of its better keeping qualities. The potency of the liquid vaccine should be checked periodically.

The conference recommended a review of the international quarantine regulations in view of the fact that smallpox "may occur in individuals possessing valid vaccination certificates".

Anti-Cancer Radar Tube

Soviet scientists have developed an ultrasonic "radar" tube which can cure cancerous tumours in their earliest stage of development, Tass news agency reported recently.

The agency, said the "bioradar" tube, invented by the Soviet Science Academy's Biophysics Institute, was better than an x-ray because it could "see" through bones and light tissues and determine the structure of foreign substances in the body.

The tube is said to be so effective that it can detect cancerous growth anywhere, even in the eye, Tass said.

The tube sends ultrasonic waves into the body and those which encounter hardness bounce back on to the

sending plaque and are then converted into electric signals to form a picture on the screen.

Annual Suicides in Britain

In U.K. 5,000 people commit suicide every year; of them 3,000 are male.

This information was given by Dr. John Pemberton of the World Health Organisation at a seminar on Public Health Nutrition opened in Calcutta on 16-11-60. The seminar was held at the All-India Institute of Hygiene and Public Health.

Dr. Pemberton, who was speaking on the "Epidemiology of mental diseases" with particular reference to the problem families in U.K. stressed that the epidemiology of mental illness was rather uncertain.

Sterilising Surgical Sutures by Gamma Rays

An important Australian advance in the technology of medical supplies is the use of gamma rays for the sterilisation of surgical sutures. In the past sutures have been sterilised with chemicals or dry heat, but these methods have some disadvantages, particularly in the case of dry heat which often destroys the natural quality of the suture and leaves it brittle.

Tests conducted by the Bacteriological Department of the University of Melbourne have shown that a certain radiation dosage gives absolute sterility. Other support for the process has come from the medical director of a large hospital in Melbourne.

Congress of the European Society of Haematology

The 8th Congress of the European Society of Haematology will take place from 28th August to 2nd September, 1961, in Vienna, Austria, under the presidency of Dr. A. Hittmair.

The official languages of the Congress are German, English and French. The main subjects of the scientific sessions: Lymphocyte, Cytology and Cytochemistry, Radiation Damage, Anaemia, Leukaemia, Immune Haematology, Haemostasis and Wound Healing, Plasmachemistry.

In addition, communications in the whole field of Haematology may be submitted. Further, a series of panel discussions will be held. A conference on Blood Transfusion and Serology is planned within the framework of the Congress. The scientific sessions will be held in the main building of the University of Vienna.

Two typed copies of the proposed lectures and communications should be submitted, with a maximum of 300 words, in German, English or French. The time limit is 20 minutes for lectures and 10 minutes for communications, which must be strictly adhered to.

Further information may be had from the Secretary General of the Congress Prof. Dr. H. Fleischhacker, Vienna IX, Frankgasse 8.

International Conference for the Study of Living Conditions

The Third International Conference of the International Medical Association for the Study of Living Conditions and Health will be held on 29th, 30th September and 1st October 1961 in St. Vincent, Aosta Valley (near Turin), Italy.

The preliminary programme consists of:

I. *Public Health as a Factor in Economic Development*

1. Rural Endemics and Agricultural Productivity.
2. The Organisation of Rural Medical Services and Economic Development.

II. *The Influence of Economic Development on Health*

1. Development of Agrarian Economy and the Fight Against Rural Endemics.
2. Industrial Development and its Eventual Hazards for Public Health.

III. *Conclusions: Health Problems and Planning of Economic Development*

Further information can be obtained from: General Secretary, International Medical Association for the Study of Living Conditions and Health, Burggasse 71/1/6, Vienna 7, Austria.

International Congress of Dietetics

The III International Congress of Dietetics will be held in Church House, Westminster, London, S.W. 1 from Monday, July 10th until Friday, July 14th, 1961, inclusive.

The theme of the Congress will be Tradition, Science and Practice in Dietetics.

The Congress will be open to members of Dietetic Association or allied professions throughout the world. The registration fee for all members will be £6. 6s. 0d. (U.S. $18.00). This fee will entitle members to attend all the scientific sessions, to join discussion groups and professional visits, to receive a copy of the Congress Proceedings. Additional information may be had from the Organising Secretary, 3rd International Congress of Dietetics, 251 Brompton Road, London, S.W. 3, England.

World Congress of Psychiatry

The Third World Congress of Psychiatry will be held in Montreal June 4-10, 1961, under the auspices of the Canadian Psychiatric Association and McGill University.

An estimated 3,000 psychiatrists, psychologists and other professional workers concerned with the prevention and treatment of mental illness and with related research are expected to attend the congress, which will attract representatives from 62 nations.

"So many vital interests and new ideas are in ferment in psychiatry today that no one theme could encompass the multitude of activities to be discussed at the congress," said Dr. D. Ewen Cameron, the Chairman of the Organising Committee.

The first congress was held in Paris in 1950 and the second in Zurich in 1957, when psychiatrists from almost every country met to discuss and exchange ideas about schizophrenia, the illness which fills one-fifth of all hospital beds throughout the world.

Annual Venereal Disease Symposium

The Twelfth Annual Venereal Disease Symposium will be held at the Hotel New Yorker in New York City on April 13 and 14, 1961. Sponsored jointly by the American Venereal Disease Association and the Public Health Service, the Symposium will follow a Venereal Disease Seminar for public health personnel which begins on April 10.

Internship and Residency Training in Canada

Applicants for Internship and Residency training in Canada are requested to note that recent communications received from Hospitals in Canada state that they have made it obligatory for Foreign Medical Graduates to pass the E.C.F.M.G. Examination before they apply for Internship or Residency appointments to Hospitals in Canada beginning with the term commencing July 1, 1961.

With this restriction imposed, the I.M.A. cannot recommend the names of candidates whose applications were received for training in Canada, till such time as and when they pass the E.C.F.M.G. Examination.

U.S.S.R. Develops New Treatment for Chronic Nervous Diseases

The Soviet Neurosurgery Scientific Research Institute has reported a new method of surgical treatment for chronic diseases of the central nervous system, such as Parkinson's Disease, Tass reported. The method, reported to the presidium of the Academy of Medical Sciences of the U.S.S.R., is introducing a thin pipe into deep-seated parts of the brain, through which a small amount of alcohol is passed, destroying the affected nerve cells. Precise calculations, using special apparatus, are needed.

Tass said that more than 70 operations had been carried out under Dr. Boris Egogov, member of the Academy, and were highly effective. It warned, however, that complete cure could not always be expected, particularly in the later stages of the disease. Symptoms of these central nervous system diseases were a constant tremor of the entire body, general rigidity and involuntary movements.

Eradication of Malaria

The United States Government has given a further grant of Rs. 4·9 crores to India's malaria eradication programme. This brings the total U.S. aid to the programme to Rs. 44·8 crores.

Under an agreement recently signed between the Governments of India and of the United States, the grant will be utilised for the purchase abroad of approximately 16,730 tons of DDT powder, 100 pick-up trucks with spare parts, and drugs used in the treatment of malaria.

Since 1953 the United States has met most of the foreign exchange needs of the campaign against malaria. In addition to dollar grants, the United States has made available to the malaria eradication programme rupees acquired through the sale of agricultural commodities shipped to India under Public Law 480.

G. J. Watumull Memorial Awards

The Distribution Committee of the Watumull Foundation of Honolulu, Hawaii, announces the establishment of 10 Annual Awards in memory of Gobindram J. Watumull, Founder, to nationals of India who shall have distinguished themselves in some way by outstanding original research or service in any of the following categories that came to a successful conclusion in the year prior to the award. The opening of nominations for the awards will take place annually on June 26th, the birthdate of G. J. Watumull. The Winners of the first awards will be announced on June 26, 1961, the 70th anniversary of his birth in Hyderabad Sind, now part of Pakistan. Presentation of the prizes will take place at a suitable ceremony in New Delhi on or about November 26, 1961. Presentation will take place each year approximately 5 months after the awards are announced. The value of each award is Rs. 5,000·00.

Categories: Sciences—Medicine, Biochemistry, Microbiology, Physics, Agriculture, Astronomy, Mathematics, Nutrition.

Humanities:—Education—including Adult Literacy, Journalism, Economics, Sociology, Social Welfare, Architecture, Family Planning, Community Leadership.

Any Indian citizen, male or female, residing in India who has done outstanding work in any of the announced categories is eligible to be nominated for an award.

Colleagues and professors of candidates, civic leaders, professional societies, and/or established experts in the various fields, may nominate a candidate. Nominators may secure application blanks by writing to: Mrs. B. L. Sahney, 14, Talkatora Road, New Delhi. Further information may be available from her.

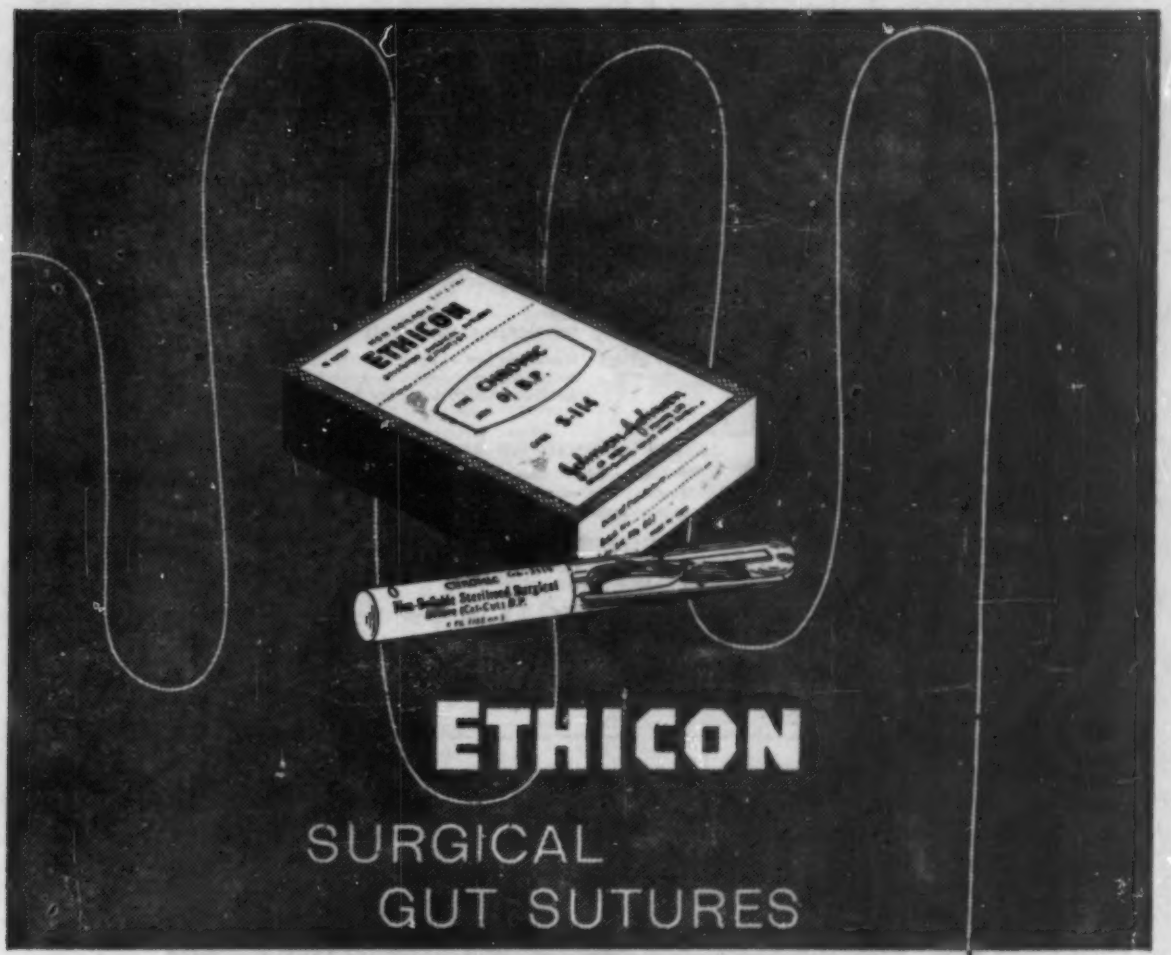
Cancer in India

About 1·8 million people suffer from cancer in India, according to Dr. Subodh Mitra, Dean of the Medical Faculty and Vice-Chancellor of Calcutta University.

Dr. Mitra, who was speaking at a seminar on Public Health, held recently at the All India Institute of Hygiene and Public Health said that 2·6 per cent of total deaths in Calcutta were due to cancer. Cancer of the female genital organs occupied the topmost position amongst all types of cancer. There was no difference in the rate of incidence of cancer in the urban and rural areas. After heart disease cancer was the second largest killer of mankind.

U. G. C. Grant for New Institute

The University Grants Commission has sanctioned a non-recurring grant of Rs. 17,13,000 for the establishment of the Post-Graduate Institute in Basic Medical Sciences of Calcutta University. The West Bengal Government has offered land and a non-recurring grant of Rs. 8,57,000 for the purpose. The U.G.C. will also bear 50 per cent of the recurring expenditure, estimated at Rs. 1,70,000. The other 50 per cent will be shared by the State Government and the University.



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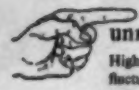

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The State Government, it is learnt proposes to allot about 10 cottahs of land for construction of the institute building inside the Sukhlal Karnani Memorial Hospital compound in the Bhowanipore area, Calcutta. Discussing the scheme, a prominent member of the University Senate commented that the land offered by the Government would be too small for a research and teaching institute with immense possibilities of future development and expansion.

Public Health Problem

The Union Health Minister said in New Delhi on 14-11-60 that a preventive approach to public health problems would have to be given precedence over a purely curative one.

The Minister, who was inaugurating the fourth conference of public health engineers at Vigyan Bhavan, said that environmental hygiene was very rightly assuming an all-important place in our public health plans. But he regretted that much attention had not yet been given to this aspect of the problem in the rural areas.

He was of the view that rural water supply programmes had not received due attention. Unless they stepped up their activities and expanded their programmes suitably, the problem might well "overwhelm us with its sheer magnitude".

High Priority to Urban Water Supply and Sanitation Urged

The Central Council of Local Self-Government at its sixth meeting at Bangalore on 9-11-60 urged that high priority should be accorded to urban water supply and sanitation programme by the Government of India, the Planning Commission and the State Governments.

It observed that the allocation of Rs. 78 crores for this programme under the Third Plan was inadequate and recommended that it should be increased substantially.

The Council felt that if the required amount could not be obtained under the provision of the Plan, it was essential to explore ways and means of augmenting resources and raising additional funds from the open market to enable State Governments to supplement their resources over and above what would be available under the plan.

Recognising the need of financial assistance by way of subsidy both from the States and Central Governments for urban sewage schemes, the Council suggested that the amount of subsidy from the Centre should be 33⅓ per cent of the cost of such schemes.

The Council also considered the problem of rural water supply and felt that as there was no provision under the national water supply and sanitation programme to cover piped water supply to rural areas the amount of Rs. 2 crores provided for the carried-over schemes under the Second Plan would result in a large vacuum being created in the implementation of more complicated and difficult schemes in all the States. The Council urged that it was essential to make provision of an amount which will cover piped water supply to individual villages and not confine it to groups of villages.

Adulteration of Food

The Union Health Minister, inaugurating a three-day seminar on "prevention of food adulteration" said the annual report on the working of the Food Adulteration Act for the year 1958 received from the State Governments showed that the percentage of adulteration varied from 06·7 to 15·9, giving an all-India average of 29·1. "This abundantly goes to show that the Act is not being vigorously implemented."

He added that the Act provided a maximum punishment but no minimum punishment. It was possible that fraudulent vendors might be dealt with lightly under the Act. To overcome this difficulty, the Council of Health Ministers has resolved that the minimum punishment should be a fine of Rs. 500 and no maximum punishment should be prescribed.

Industrial Health Service in India

The need for a comprehensive industrial health service in India has been stressed in the recommendations made by the Technical Committee, appointed by the Union Ministry of Labour and Employment, to suggest modifications in the list of occupational diseases, etc.

The committee recommended that all diseases to be included as compensatable in the Workmen's Compensation Act, Schedule III, should also be made notifiable under the relevant labour laws, such as the Factories Act and the Mines Act.

The 11-man committee was headed by Dr. M. N. Gupta, Deputy Chief Adviser, Factories (Medical), New Delhi.

According to the committee, silicosis, asbestosis, bagassosis and coal miner's pneumoconiosis, poisoning by halogen derivatives of hydrocarbons of the aliphatic series, carbon disulphide poisoning, occupational cataract due to infra-red radiations, occupational dermatitis and poisoning by nitro and amido derivatives of benzene and its homologues can be included in the list of compensatable occupational disease.

The committee also has recommended that provisions should be made to encourage research into problems of suppression of dust in mines and factories and appointment of special dust officers to carry out routine dust surveys in mines and factories.

The committee has also touched upon many allied problems and suggested remedies. These recommendations, if and when implemented, will have a far-reaching effect on the economy of Indian industries.

CORRESPONDENCE

The Editor is not responsible for the views expressed by correspondents

Sexual Irregularities

SIR,—Two important reports on sexual irregularities were published in England in 1957. They were :

1. The Report of the Royal Commission on Marriage and Divorce—Three opinions emerged : (i) divorce should

be abolished, (ii) the present legislation is adequate and (iii) divorce should take place by common consent of the parties without the intervention of the courts (*Medical Annual*, 1957).

(The present legislation in England has 3 grounds for divorce: (i) desertion, enacted in 1938 and at present the most frequent ground, (ii) adultery coming second and (iii) cruelty coming a bad third.)

2. The Report of the Royal Commission on Homosexual Offences and Prostitution—It is the well-known 'Wolfenden Report' from which emerge 4 points: (i) nowadays poverty does not impel women to become prostitutes; most prostitutes follow their trade primarily because they like it; sterner measures are indicated against them and their organisers; (ii) laws against male homosexuality are ineffective and lead to blackmail besides; (iii) acts of gross indecency between consenting adult males should cease to be criminal offences; and (iv) few confirmed male homosexuals are curable and are treated with unnecessary severity when given a prison sentence (*Medical Annual*, 1958).

Our recent legislation concerning divorce amongst the Hindus has not yet had sufficient trial and a comparison is not possible. Besides, the transaction of marriage itself is not comparable yet in the majority of cases. The medical profession in India, however, has an interest in the divorce for the same reasons as the same profession in England. When all is said and done the maladjustments in psychology are our concern and responsibility, and from the maladjustments arises the divorce anywhere (excepting the royal families demanding a male heir). Incidentally, in our law, the adultery must be habitual.

The legislation on homosexuality amongst males in our country is a matter of 'book transfer' from pre-independence days. Obviously it needs revision.

The lead given in the Wolfenden Report summarised above has been recently followed frankly and fully in an editorial (1955) in the *Lancet*. The editorial is based on an equally frank and full, though anonymous, communication by an experienced medical practitioner (1959) who is a homosexual himself. The notable points of this letter are: (i) The homosexual medical practitioner has discussed the subject intimately over the past 30 years with several hundred homosexual men of many nationalities, colours, cultures and creeds, and provided typical histories of 16 cases. (ii) The cause of homosexuality is still unknown. (iii) Some men are wholly homosexual and incapable of heterosexuality. (iv) The main sexual pattern is laid down in the early years of life. (v) Homosexuals are reluctant to seek medical advice because they believe that most medical men are ignorant and prejudiced like laymen. (vi) In Britain between 1½ and 2 million men are predominantly homosexual. (vii) The habit does not seem to impose any serious handicap as a rule; alcoholism, distress of wasted youth and suicide are exceptional, but do occur (hence the importance of history). (viii) Lesbianism, fornication, adultery, rape and even murder can be discussed objectively, usually, but homosexuality rarely.

The abnormality (or temperament ?) behind the homosexuality needs serious study. The present writer (S. D. S. Greval) broke fresh ground when he recast this item in the 10th edition of Lyon's Medical Jurisprudence for India, in 1953 (Greval, 1953). The casement diaries, published recently (authenticity doubtful) are well worth a study. One entry refers to a suicide of a high rank who was homosexual (Parmiter, 1960).

To take the first item of the Wolfenden Report last, for emphasis, our social workers are pampering the prostitutes, contrariwise. They provide for these fallen women homes, recreations, excursions and garden-parties (including, in one state, an annual garden-party in the Government House, Presentation at the Court)! The plea of poverty cited and accepted as a matter of course remains the curse of the East, and makes the social worker run counter to well-considered findings from elsewhere as a matter of grace. I am, etc.

S. D. S. GREVAL
I.M.S. (RETD.), LT.-COL.
Calcutta

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Idem—Ibid (1958), John Wright & Sons Ltd., Bristol.
MEDICAL PRACTITIONER—*Lancet*, **2**: 1077, 1959.
PARMITER, G. De C.—*Quart. Rev.*, **298**: 221, 1960.

Survival after Bite of a Venomous Snake (Cobra)

SIR,—On 31-8-60, B. B. R., Nepali male aged 41 was brought to D. I. B. Hospital at about 11-35 A.M. with history of snake bite approximately 20 minutes before arrival. The bite was on the outer aspect of the right ankle joint. It bore two fang marks half a centimetre apart. There was slight oozing from the wound. Tight ligatures were applied both above and below the site of the bite. The patient was composed and showed no sign of shock. Pulse was 80 per minute, with good volume and tension. The general condition was fair.

The patient answered questions promptly and to the point. He described the snake as a hooded one. It was subsequently brought to the hospital and identified as a cobra.

The site of the bite was at first bled by multiple deep incisions, and then cauterised with potassium permanganate crystals and finally dressed. Coramine 2 c.c. was injected hypodermically and polyvalent antivenin (Haffkine), 10 c.c., given intramuscularly. The ligatures were loosened for 10 minutes and reapplied. Adrenaline, 0·5 c.c., was kept ready for emergency. However, no serum reaction developed.

One hour later 10 c.c. of the antivenin was injected slowly intravenously, and the ligatures released for 20 minutes and reapplied. As the general condition of the patient remained unchanged, the ligatures were finally removed. The patient complained of pain below the ligature, where slight oedema appeared. 10 c.c. antivenin was repeated intravenously six hours later. No sign of

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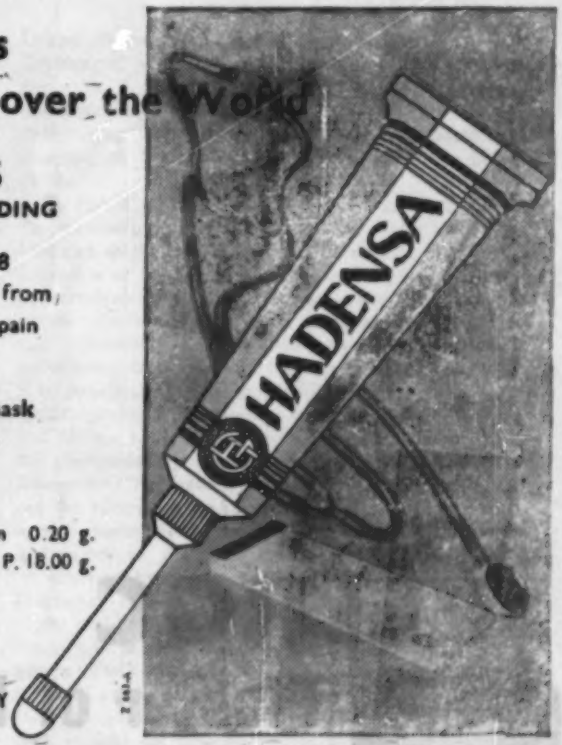

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neurological abnormality was noticed at 6 P.M. but his temperature rose to 102°F with chill, and general flushing was noticed. The latter gradually subsided after the next 24 hours. Cellulitis developed around the wound. The pulse rate was 120 per minute.

The treatment included antistine (100 mg. twice daily), penicillin (5 lac units, I.M., twice daily) and phenargan (25 mg. twice daily) for 4 days. On 4-9-60 antitetanic serum was injected after intradermal sensitivity test. The wound was dressed with S. S. magnesium sulphate on alternate days.

On 5-9-60 the general condition of the patient was fair, the wound was healing and the temperature and pulse were 100°F and 120 per minute respectively. The flushing had completely disappeared. The relative tachycardia was unaffected by treatment.

There was no primary shock and the patient kept his morale at a high level. The snake (cobra) was trapped in semi-molten pitch on the cut lid of a pitch drum. The bite did not produce any poisoning—the antivenin might have neutralised the minute trace of venom injected during the bite.

The case is interesting in that the patient survived the bite of a venomous cobra. We are, etc.

S. K. MITRA, B.SC., M.B.B.S.
Durgapur (W. Bengal). (MISS) K. SEN, M.B.B.S.

REVIEWS

Notes on Infant Feeding—By Stanley Graham, LL.D., M.D., F.R.C.P. (ED.), F.R.F.P.S. (GLAS.) and Robert A. Shanks, M.D., M.R.C.P. (LOND.), F.R.F.P.S. (GLAS.); 5th edition, 1960, E. & S. Livingstone Ltd., Edinburgh and London; 7-1/5"×4-4/5", pp. 76; 4sh. 6d. net.

This little book is a practical guide for general practitioners. In it are described the principles of infant feeding which have been practised at the Royal Hospital for Sick Children, Glasgow, for many years. Complicated methods of percentage feeding have rightly been discarded, and more practical ways requiring the minimum calculations are described, based mainly on physiological principles. The authors have very reasonably emphasised on the quality of food rather than the quantity to be given. The simple method of calculating requirements of undernourished infants based on muscular exertion, excretion, growth and basal metabolism is very illuminating.

The book will be found useful to medical students and practitioners engaged in the care of infants.

S. K. ROY

The Metabolism of Oral Tissues, Vol. 85, part I, Annals of the New York Academy of Sciences—Edited by Otto v. St. Whitelock; March 29, 1960, Published by the Academy, New York; 9"×6"; pp. 499; $4·50.

This monograph is an excellent collection of papers presented in a conference on the metabolism of oral tissues held by the New York Academy of Sciences in October 1959 under the chairmanship of Dr. Philip Person of Rutgers University. It was the first centennial celebration of the organised science of dentistry in the United States. So the volume is dedicated to Joseph Goldberger, a pioneer and an eminent scientist in this field. R. F. Sognnaes of Harvard School of Medicine has contributed an informative article on the history of the development of dental research in the united states. The rest of the articles are grouped under five different parts.

In Part I (Perspectives on the oral tissue metabolism) the chairman himself writes a review about the evolution and origin of oral tissues. He mainly elucidates the formation of bony tissues and their comparative anatomy in vertebrate groups with some analogy from invertebrates. Furthermore, he tries to explain Darwinism from this viewpoint. Krogman discusses the genetical and anthropological aspect of oral structures. He suggests that genetically speaking, dentition is inter- and intraspecific in their characters. Incisors, canines, premolars and molars have certain traits of their own to preserve the phylogenetic and ontogenetic integrity as well as sex differences. He further suggests a new approach to find out the roentgenographic cephalometry. Kalter describes and discusses the congenital malformations of the face and mouth in the offspring of inbred female mice, as an effect of hypervitaminosis A about half way through pregnancy. Shaw in his article deals with the responses of the oral tissues under experimental conditions of nutritional and metabolic variabilities. Cohen and Goldman give a detailed account of the oral tissue metabolism by the local and systemic ecological factors and the resultant clinical manifestations of certain oral diseases. Further, they explore all possible angles to find out the causes of oral disease.

Tooth tissue and their studies from different angles are the major aspects of the articles in Part II. The first paper deals with the tooth composition and caries problem and concludes with a remark that high phosphate diets will produce teeth that are less vulnerable to caries. F. Brudevold *et al.* in the next article puts forward a detailed account of the chemical (both inorganic and organic) components of the successive layers of enamel, dentine and cementum. This appears to be a new and an interesting way of analysis, in comparison to the old methods of analysing the chemistry of the entire tooth. David Scott and Marie Nylen report in their paper, the modern concepts of electron microscopy regarding dental histology and reveal many interesting and changed ideas of the present time. Otto R. Trautz reports the crystallographic studies of calcium carbonate and phosphate and furnishes much valuable information regarding the submicroscopic structure of the building elements or their orientations. The last two papers, by Kreshover and Boyd respectively, deal with the effect of metabolism in tooth formation and caries in relation to host metabolism.

Part III deals with the salivary gland and the physiological phenomena of their various secretory products. L. M. Sreebny discuss about protease, a proteolytic enzyme of salivary gland origin and records the present state of knowledge of the enzyme and its relation with other hormones. The second article by Schneyer and Schneyer contains information regarding the regulation of the salivary gland amylase activity.

The next paper of Schneider and Person deals with the oxidative metabolism of the submaxillary gland studied by means of several histochemical methods. Myant reports on the iodine metabolism of salivary glands. Schafer and Muhler study endocrine influence on salivary glands and adumbrate the recent knowledge of this problem. Very interesting findings are recorded in an extensive paper by Yosoji Ito of Japan. He claims to be successful in isolating the salivary gland hormone, parotine (from bovine parotid gland) which was first reported by T. Ogata and his associates. A brief discussion of this paper by L. Kraintz of Texas has brought forward many interesting and relevant points for future researches. Fleming reports several changes on various organs of mice as an effect of parotine treatment. The last two papers by Levi-Montalcini *et al* and J. A. English deal with the mouse submaxillary gland and the radiation effect upon the salivary gland respectively.

Part IV deals with the papers related to the tongue and oral mucosa. There are four papers in this section contributed by D. Weisberger and C. J. Fischer, J. H. Albright, D. Afonsky and lastly by G. Stein and H. Spencer. They report various aspects of studies of the buccal mucosa, gingiva tongue, etc., from electron microscopy and nutritional changes.

The last part (V) contains nine papers specially dealing with the different aspects of periodontal tissues in mammals. Gould *et al* note that ascorbic acid is essential for the maintainance of newly formed collagen, but is not essential in the formation of collagen from embryonic mesenchimal tissue. Engel *et al.* put forward a combined report of their researches of the morphologic, chemical and physiologic studies on a variety of connective tissues with special reference to its implication in periodontal disease. Laskin and Engel discuss in their papers the relation between the metabolism and structure of bone. M. S. Burstone observes histochemically, the enzymatic processes of bones and teeth. Osteogenesis in polythene tube, is the aspect of study by W. J. Linghorne and his observation leads to a lot of controversy. Lisanti studies the nature and site of the hydrolytic enzymes in periodontal tissues. He concludes that alkaline phosphatase, beta-D glucoronidase, galactosidase, glucosidase and acid phosphatase have got special regions of distribution and their level elevates in the areas and foci of inflammation. Macdonald *et al* report the bacterial mechanism in periodontal disease. Bertram Eichel gives a nice account of the oxidative enzymes of the gingiva and discusses some of these significance and implications. The last paper by S. S. Sthal is on the interaction between local and systemic factors on the genesis of periodontal lesions.

In general the book under review presents sufficient evidence to show that the conference has achieved the object for which it was called. It has brought to light the monumental research progress of dental medicine in the United States. The editors and the authors deserve to be congratulated and thanked for their efforts in bringing out this excellent treatise which will be of immense help to dental medical students and research workers in the field of oral tissue metabolism.

A. GHOSH

OBITUARIES

Dr. P. M. Kale

Dr. P. M. Kale passed away after prolonged illness on October 27, 1960, at Khamgaon.

He was born in 1886 at Lonar, District Buldana. He completed his medical education at Hyderabad (Dn.) and became Hospital Assistant in C. P. and Berar Medical Service. While in service he passed the L. M. & S. (National) at Calcutta. He resigned in 1918 and started private practice at Khamgaon.

Good nature and genial temperament made Dr. Kale very popular. He took keen interest in social activities, sports and games. He was president of Nagar Congress Committee and president of Taluka Local Board and a member of the Municipal Committee for many years. Also he became president of Nagar Hindu Maha Sabha and was Nagar Sangh Chalak till his death.

He took active part in starting Medical Association at Khamgaon in 1937. He was its first president. After it was affiliated to I.M.A. in 1947, he was also its president.

His death is a great loss to the whole of Khamgaon town and the Association.

DR. P. M. KALE

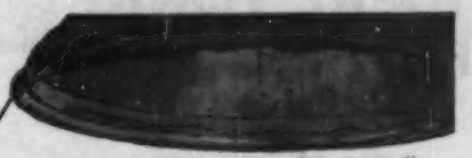
LT.-COL. D. G. MARATHE

Lt.-Col. D. G. Marathe

Dr. D. G. Marathe was born on December 22, 1901. He graduated from the Bombay University in 1929. In 1930, he joined the army medical services of the Gwalior State. He was a popular doctor in the army. His services were also appreciated by the State and he was promoted to the rank of Lt. Col. before retirement.

After retirement in 1951, Dr. Marathe started private practice in Janakganj Lashkar and in a short time became very popular. In 1959, he had a heart attack and later he developed obstructive jaundice and cancer. He was removed to Bombay for an operation but unfortunately he expired there on 28-9-60.

Dr. Marathe was an active member of the Gwalior Branch, I.M.A.



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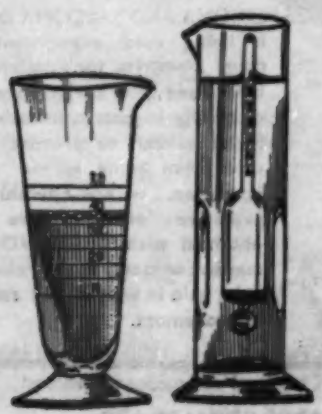

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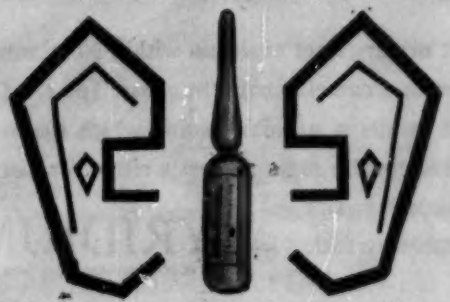

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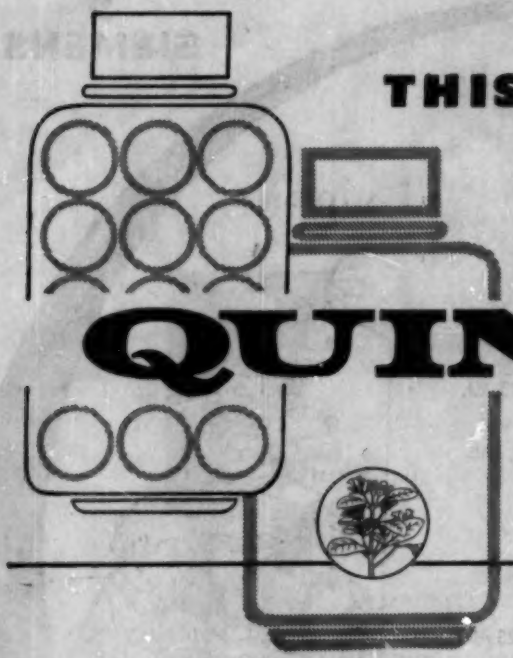

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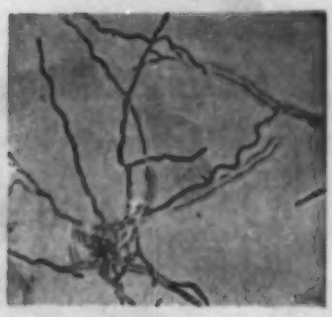

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